Computational Toxicology

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U.S. Environmental Protection Agency

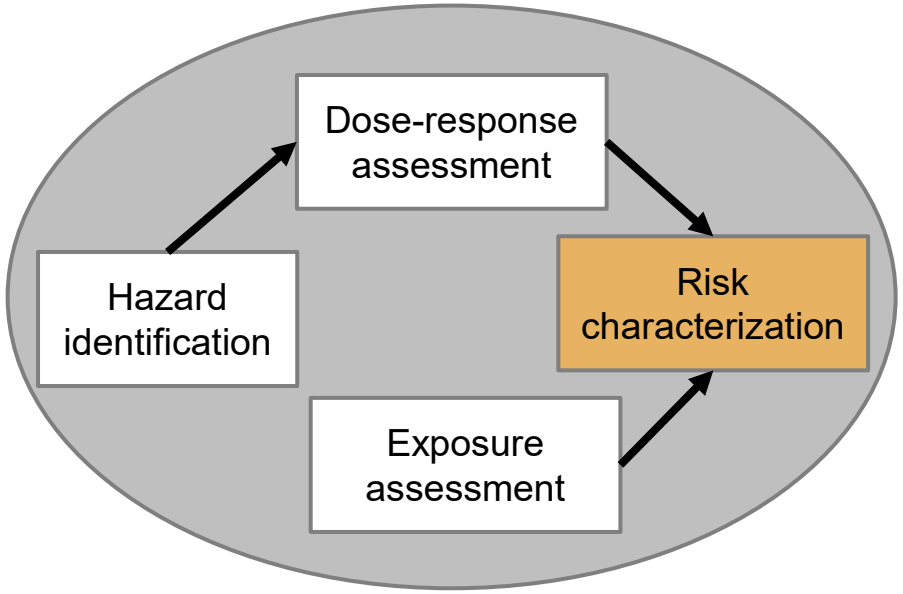
The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

Dr. Nisha S. Sipes has over 10 years of experience developing and using bioinformatics and computational toxicology approaches to translate high-throughput screening (HTS) data and other new approach methodologies (NAMs) to better estimate *in vivo* likelihood of chemical-biological interaction. She currently serves as the Assistant Center Director for Research Translations & Program/Regulatory Support for the US EPA Center for Computational Toxicology and Exposure (CCTE), where she facilitates the translation of CCTE research for use in decisions and provides scientific and technical expertise to internal and outside stakeholder groups.

Learning Objectives

- Why Alternatives are Needed
- Understand Computational Toxicology Concepts, Tools, and Approaches
  - New Approach Methodologies (NAMs)
  - Read-across
  - High-throughput *in vitro* assays
  - *In vitro* to *in vivo* extrapolation
  - Rapid exposure predictions
- Computational Toxicology in Practice and Potential Use

What Do You Need for Traditional Chemical Risk Characterization?



Data needs

- Chemical characterization
- Hazard; human health and ecological data, *in vivo* data, biological targets (effect), dose-response characterization (dose)
- Toxicokinetics
- Exposure; exposure scenarios, exposure levels

How to obtain

- Animal models + exposure sampling

Why Is There a Need for Alternative Approaches?

- Too many chemicals to test with standard animal-based methods
  - >40,000 active substances on US EPA Toxic Substances Control Act (TSCA) inventory
    https://www.epa.gov/assessing-and-managing-chemicals-under-tsca
  - We do not have detailed exposure information
- Traditional toxicity testing is costly and time consuming
  - Natural or industrial disasters (e.g., Gulf of Mexico oil spill)
- Traditional animal-based testing has issues related to ethics and relevance
  - Mechanistic understanding
  - Physiology comparisons (e.g., respiratory physiology in rats)
- Looking into new ways to address these problems

Computational Toxicology

- Gathering, integrating, and evaluating data and information using mathematical and computer-based approaches to better understand chemical hazards and risks to human health and the environment

- Typically refers to non–*in vivo* toxicological tools and approaches
  - New Approach Methodologies (NAMs)—*in silico*, *in chemico*, *in vitro*, hazard + exposure

- Some tools and approaches are already used in hazard and risk assessments
  - E.g., Quantitative Structure-Activity Relationships (QSARs), *in vitro* assays used in lieu of *in vivo* assays

Kavlock RJ, et al. Toxicol Sci. 2008;103(1):14-27.
Kleinstreuer NC, Tetko IV, Tong W. Chem Res Toxicol. 2021;34(2):171-175.

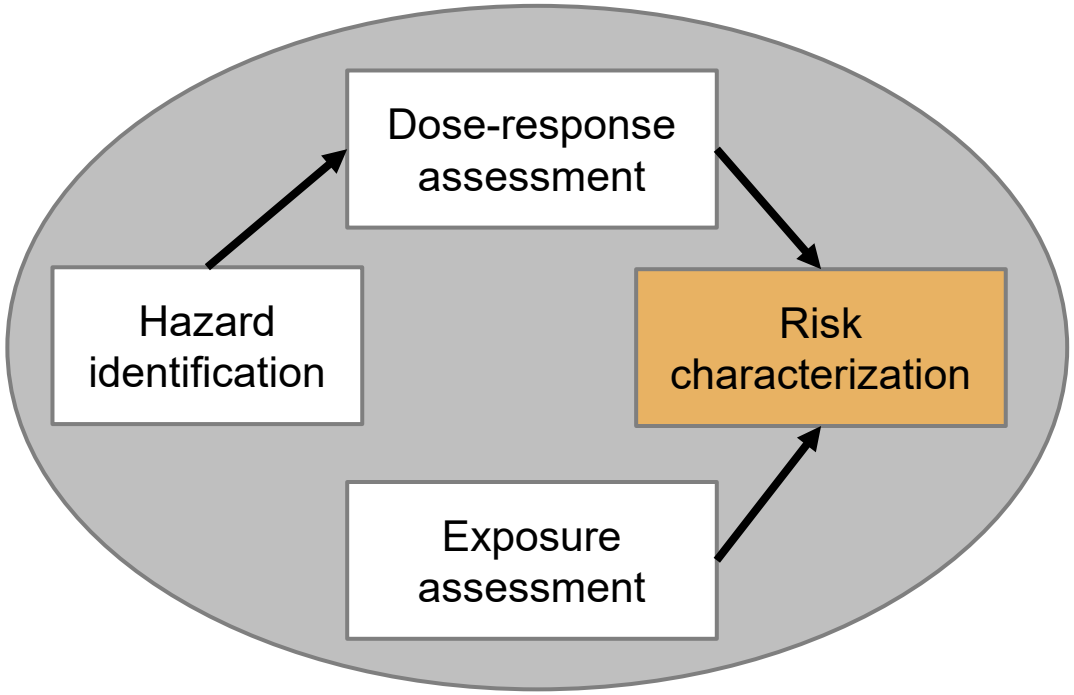
New Approach Methodologies (NAMs)

National Academies of Sciences, Engineering, and Medicine 2017
https://doi.org/10.17226/24635.

- Adverse outcome pathways (AOPs)
  Pathway identification and knowledge integration
- *In silico* (e.g., QSAR and read-across)
  Estimate effects and doses
- *In vitro* assays
  - *Broad / screening (transcriptomics, cell painting)*
  - *Targeted (receptors, enzymes)*
  - *In vitro PODs, modes/mechanisms of action*
- *In vitro* toxicokinetics
  Allow conversion of an in vitro *POD to* in vivo *(IVIVE)*
- Computer models
  Integrate multiple in silico and in vitro data streams
- Databases of existing traditional toxicology data
  Enables training and validation of NAM models

Kavlock RJ, et al. Toxicol Sci. 2008;103(1):14-27.

How Can We Use Alternative Approaches in Risk Characterization?



1. *In silico* read-across (data gap analysis)

2. Hazard assessment (ID and dose-response)
   a. *In vitro* assays
   b. Making sense of *in vitro* potencies using *in vitro* to *in vivo* extrapolation (IVIVE)

3. High throughput exposure assessment

4. Risk characterization

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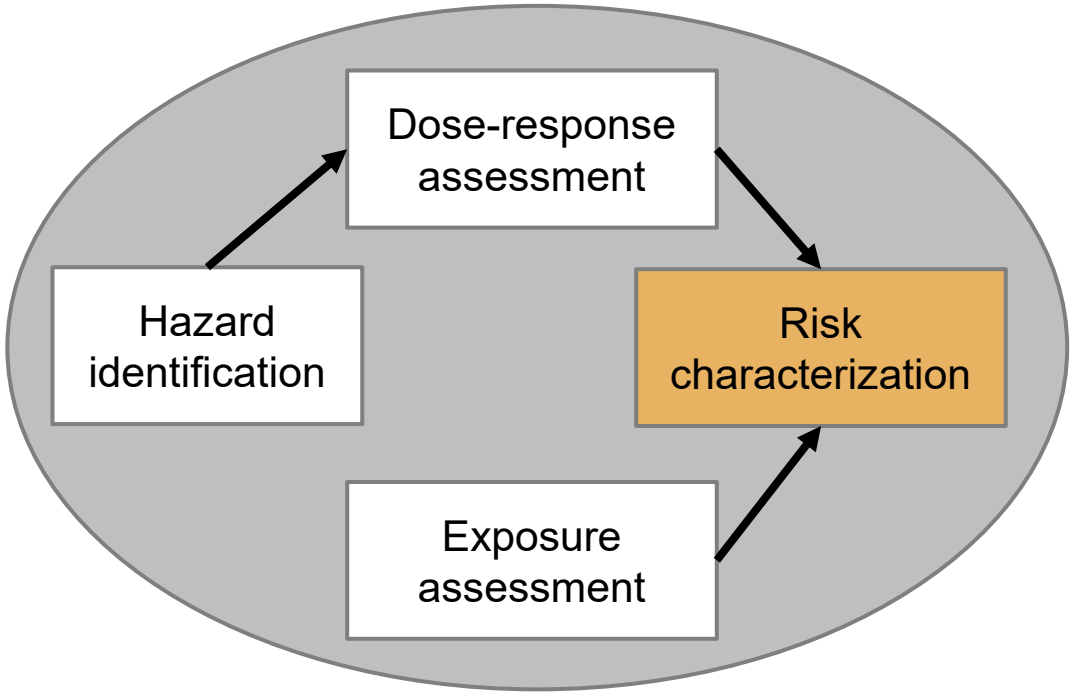

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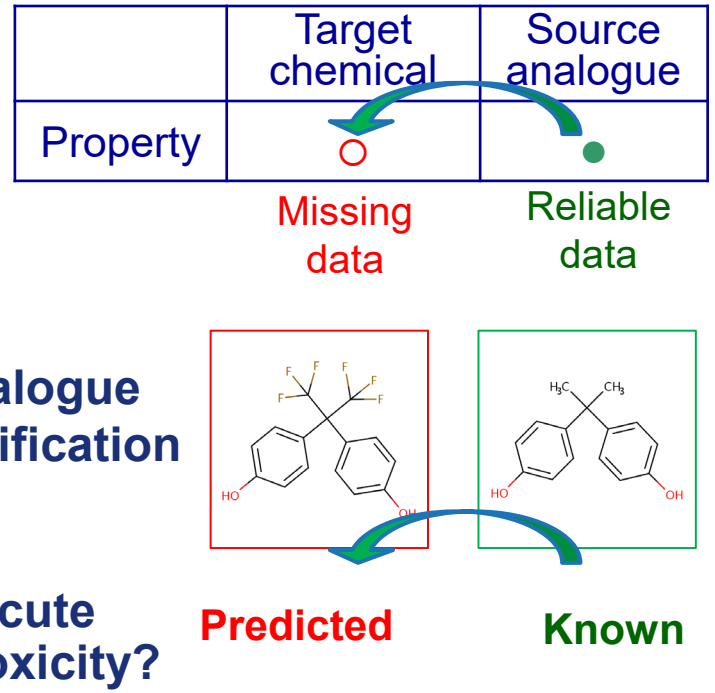
In Silico Read-Across (Data Gap Analysis)

- Read-across describes the method of filling a data gap whereby a chemical with existing data (source analogue) is used to make a prediction for a "similar" chemical (target chemical)

- Need curated chemical structures, physical-chemical properties

- Several freely available tools
  - Including GenRA in the EPA CompTox Chemicals Dashboard

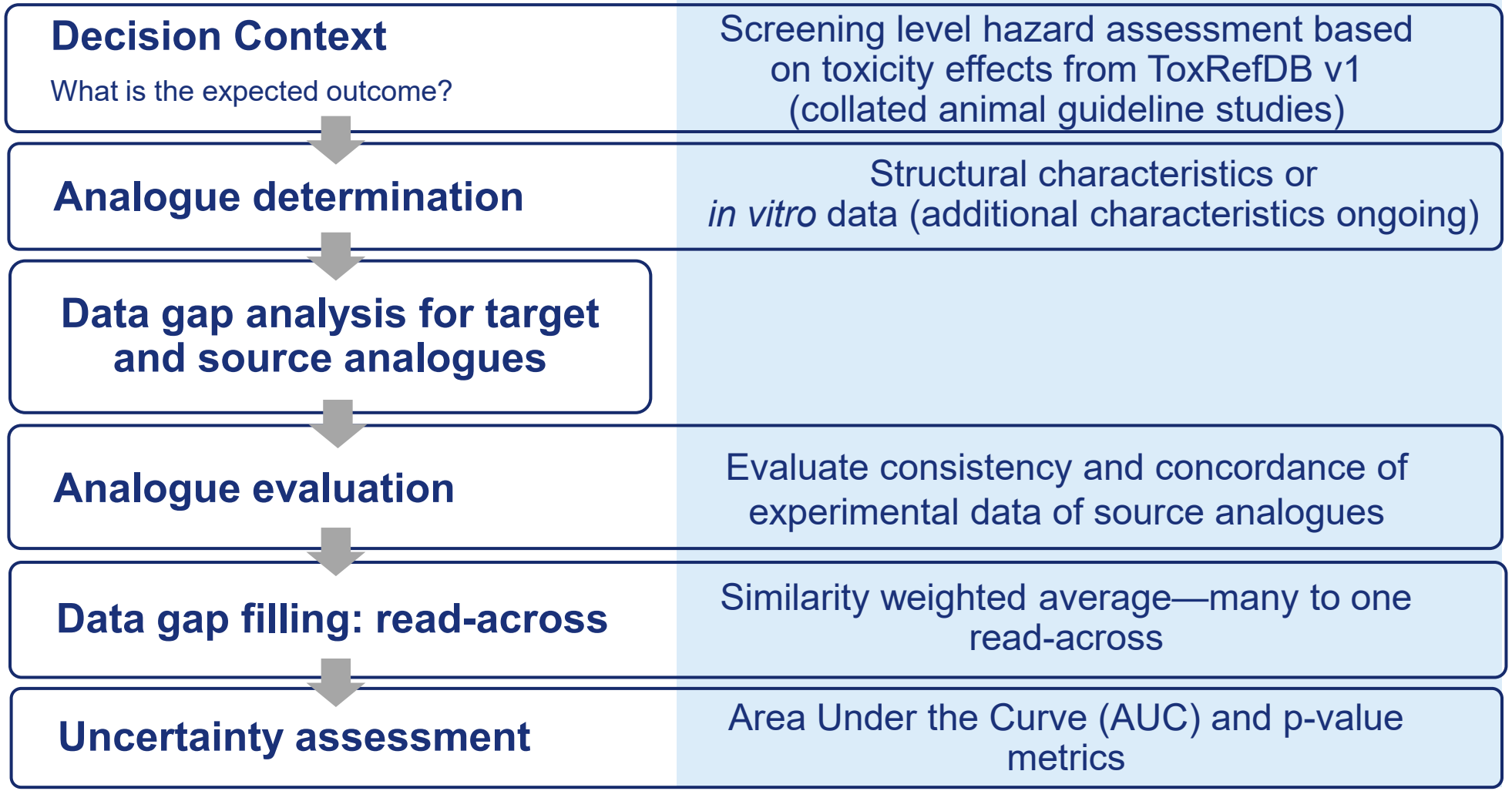


G Patlewicz, et. al., Comput Toxicol. 2017;3:1-18. doi:10.1016/j.comtox.2017.05.003
Shah I, et al., Regul Toxicol Pharmacol. 2016 Aug;79:12-24. doi: 10.1016/j.yrtph.2016.05.008

Read-Across Workflow

Specific for US EPA GenRA v1.0

Generalized read-across (GenRA)



Read-Across in Practice

- Valuable for chemical safety assessment
  - Read-across acceptance for regulatory purposes remains an issue
    - Difficulties addressing residual uncertainties
    - Subjective, expert-driven assessment
    - Need more experience using these tools
- GenRA is an attempt to move toward an objective read-across approach where uncertainties and performance can be quantified
- Organisation for Economic Co-operation and Development (OECD)
  - Guidance on Grouping of Chemicals (No.194, 2014)
    http://www.oecd.org/officialdocuments/displaydocument/?cote=env/jm/mono(2014)4&doclanguage=en
  - Integrated approaches to testing and assessment (IATA) case studies

Rovida, C., et al. (2021) *ALTEX*, 38(1), pp. 140-150. doi: 10.14573/altex.2010062.
Chesnut, M., et al, (2018) ALTEX, 35(3), pp. 413-419. doi: 10.14573/altex.1805081

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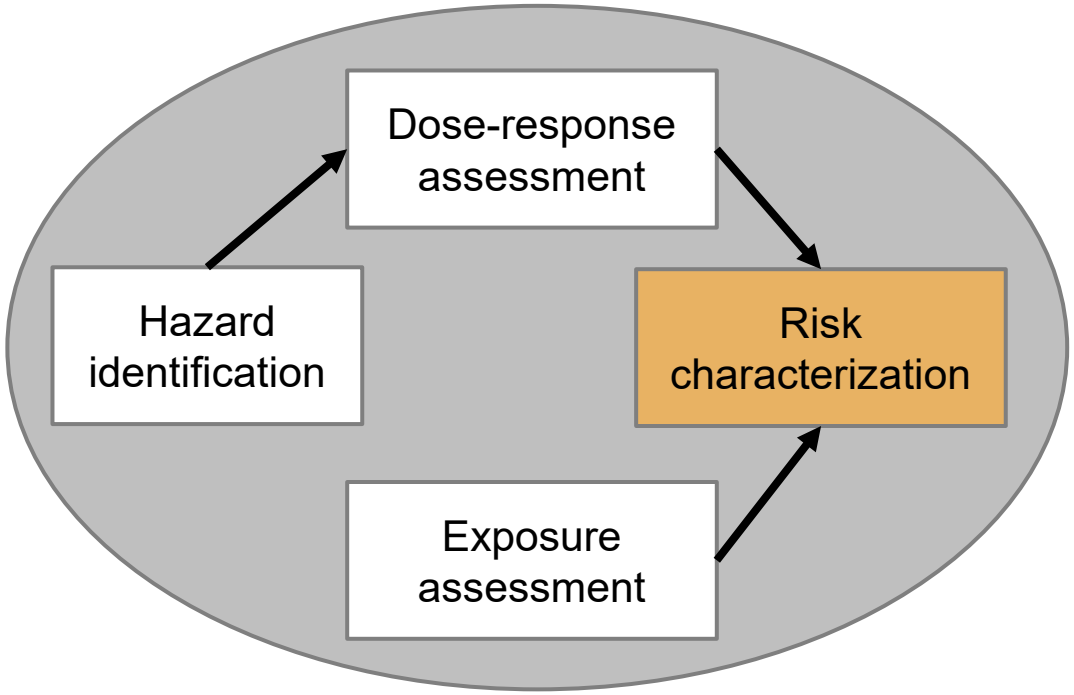

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In Vitro Assay Hazard Identification and Dose-Response

Hazard identification

Dose-response

Point of Departure (POD) corresponds to an estimated lowest effect level

In vivo

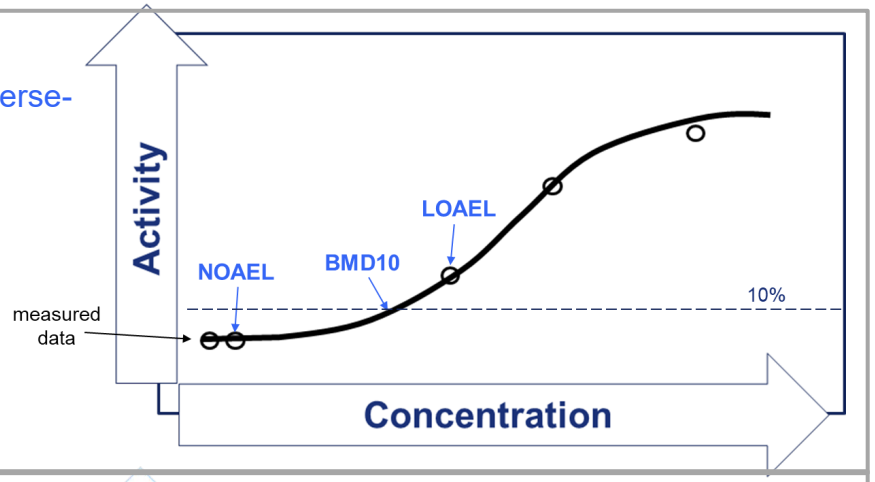
Targets & pathways (AOPs)

External Exposure → Internal Exposure

Molecular Targets — Cellular Changes — Tissue & Organ Changes — Organism Response

POD

- **NOAEL** no-observed-adverse-effect level
- **LOAEL** lowest-observed-adverse-effect level
- **BMD** benchmark dose
  - *Predetermined threshold*



In vitro

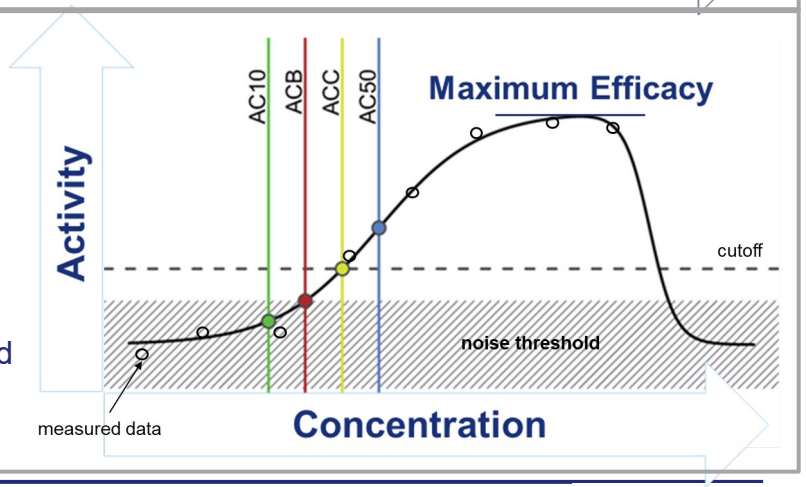
Internal Exposure

Molecular Targets — Cellular Changes — Tissue & Organ Changes

POD

- **AC10** activity concentration at 10% of maximal activity
- **ACB** activity concentration at baseline (noise)
- **ACC** activity concentration at cutoff (significance)

Across multiple assays—determined for the most sensitive *in vitro* assay



Filer DL, et al, Bioinformatics, 33(4), 2017, 618–620, https://doi.org/10.1093/bioinformatics/btw680

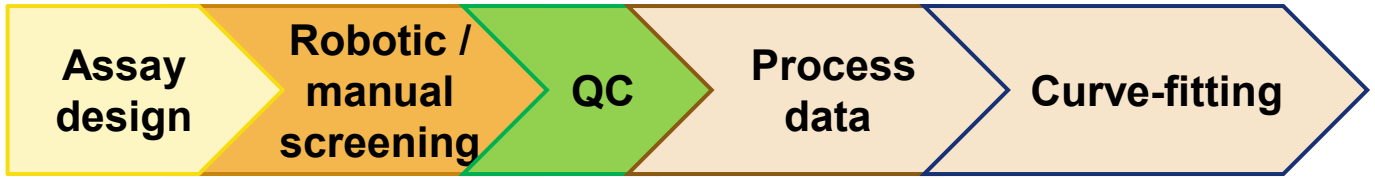
Summary of *In Vitro* Assay Types for Hazard Evaluation

- High-Throughput Screening assays (HTS)
- High-Throughput Transcriptomics (HTTr)
- High-Throughput Phenotypic Profiling (HTPP)
  - High Content Screening (HCS)
- Organotypic Models
- Microphysiological Systems (MPS)
- Small Model Organisms

High-Throughput Screening (HTS) Assays

in vitro assay

- Easily screens hundreds to thousands of chemicals
- Typically targeted to measure specific chemical-target interactions (e.g., individual receptor, enzyme reporter assays)
- Takes a coordinated (preferably automated) data analysis pipeline



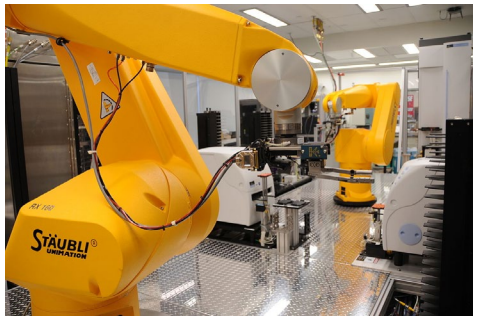
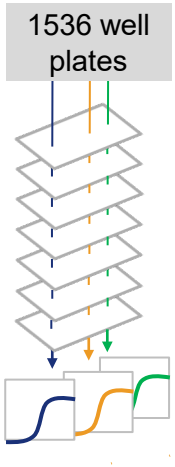


Image: https://ncats.nih.gov/news/releases/2018/tox21-strategic-plan



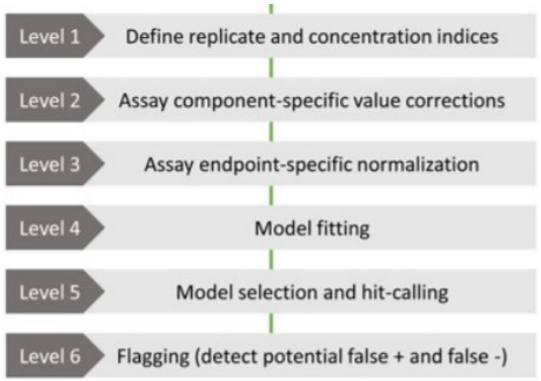
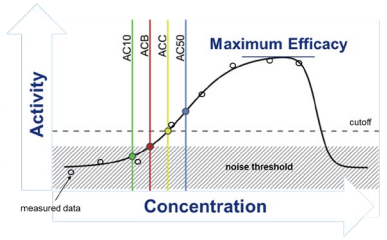
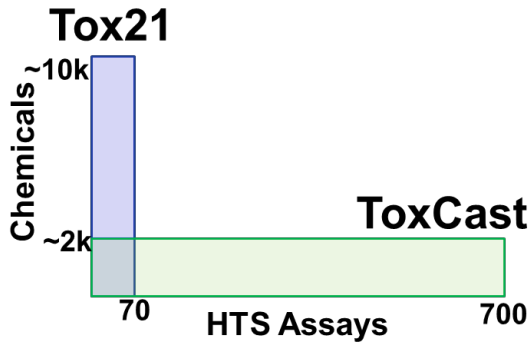


Image: https://www.epa.gov/sites/production/files/2018-04/documents/toxcastownermanual4252018.pdf





E.g., Tox21 & ToxCast HTS assays

https://tox21.gov/
https://www.epa.gov/chemical-research/toxicity-forecasting

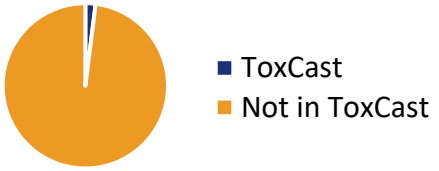
Limitations: need *a priori* knowledge of molecular targets; incomplete coverage of important pathways (i.e., biological space)

High-Throughput Transcriptomics (HTTr)

in vitro assay

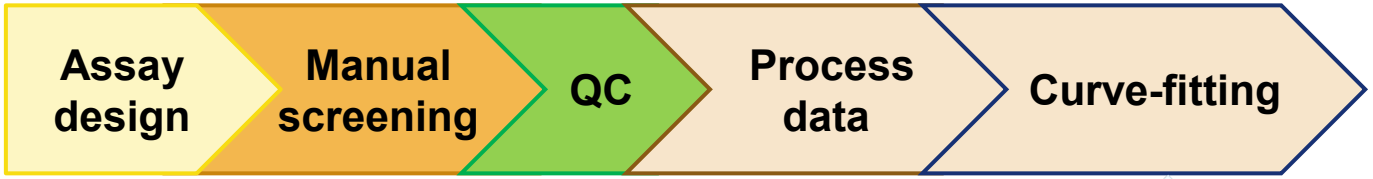
- Whole transcriptome assay measures expression of ~20,000 transcripts at once
- Increasing biological coverage over single reporter assays
- Low cost, uses purified RNA samples or cell lysates
- Scalable, targeted assay: measure transcript of interest, greater throughput than RNA-Seq, attenuate highly expressed genes

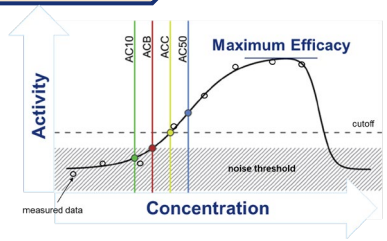
Gene Coverage



Pathway Coverage*

* At least one gene from pathway represented



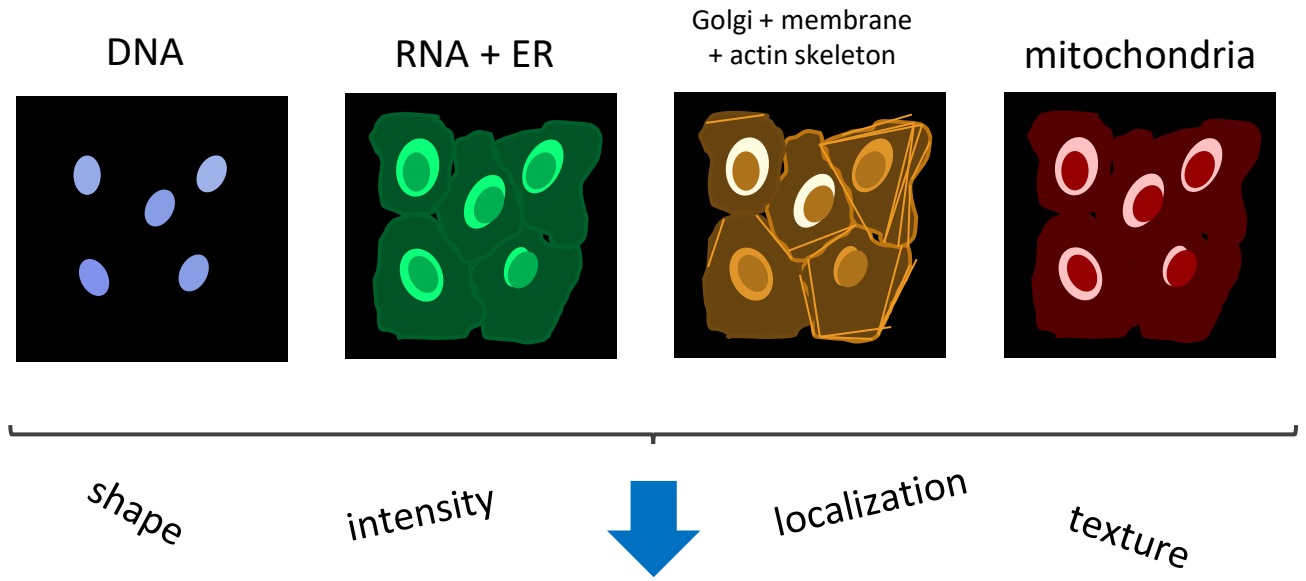


Limitation: only reveals transcript expression changes

High-Throughput Phenotypic Profiling (HTPP)

in vitro assay

- Image-based phenotypic profiling measures a large variety of morphological features of individual cells in *in vitro* cultures
- Successfully used for functional genomic studies and in the pharmaceutical industry for compound efficacy and toxicity screening



Flourescent labels
DNA: H-33342
RNA: SYTO14
ER: Concanavalin A-488
Actin: Phalloidin-568
Golgi + Membrane: wheat germ agglutinin (WGA) -555
Mitochondria: MitoTracker

High Content Screening
Cell Painting

Limitation: does not identify tissue/organ effects

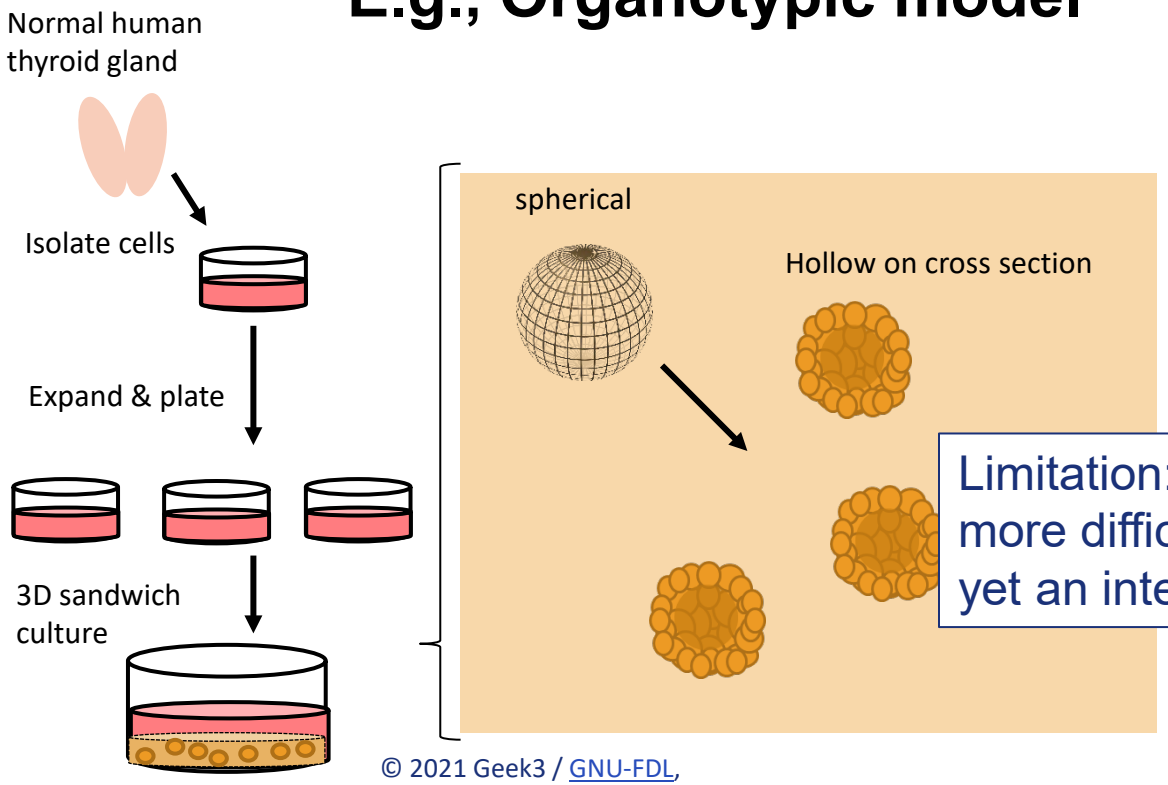
Organotypic Models and Microphysiological Systems (MPS)

in vitro assay

Three-dimensional cellular *in vitro* models

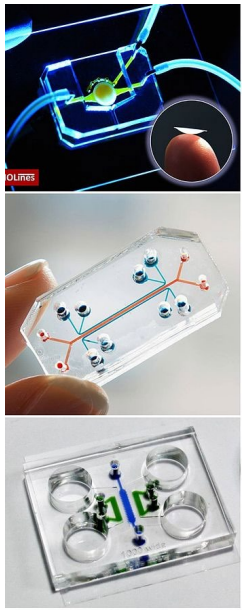
Interconnected *in vitro* models in microphysiologically relevant “chips”

E.g., Organotypic model



Limitation: low throughput; more difficult to develop; not yet an integrated system

E.g., MPS or Organ-on-a-chip



Small Model Organisms

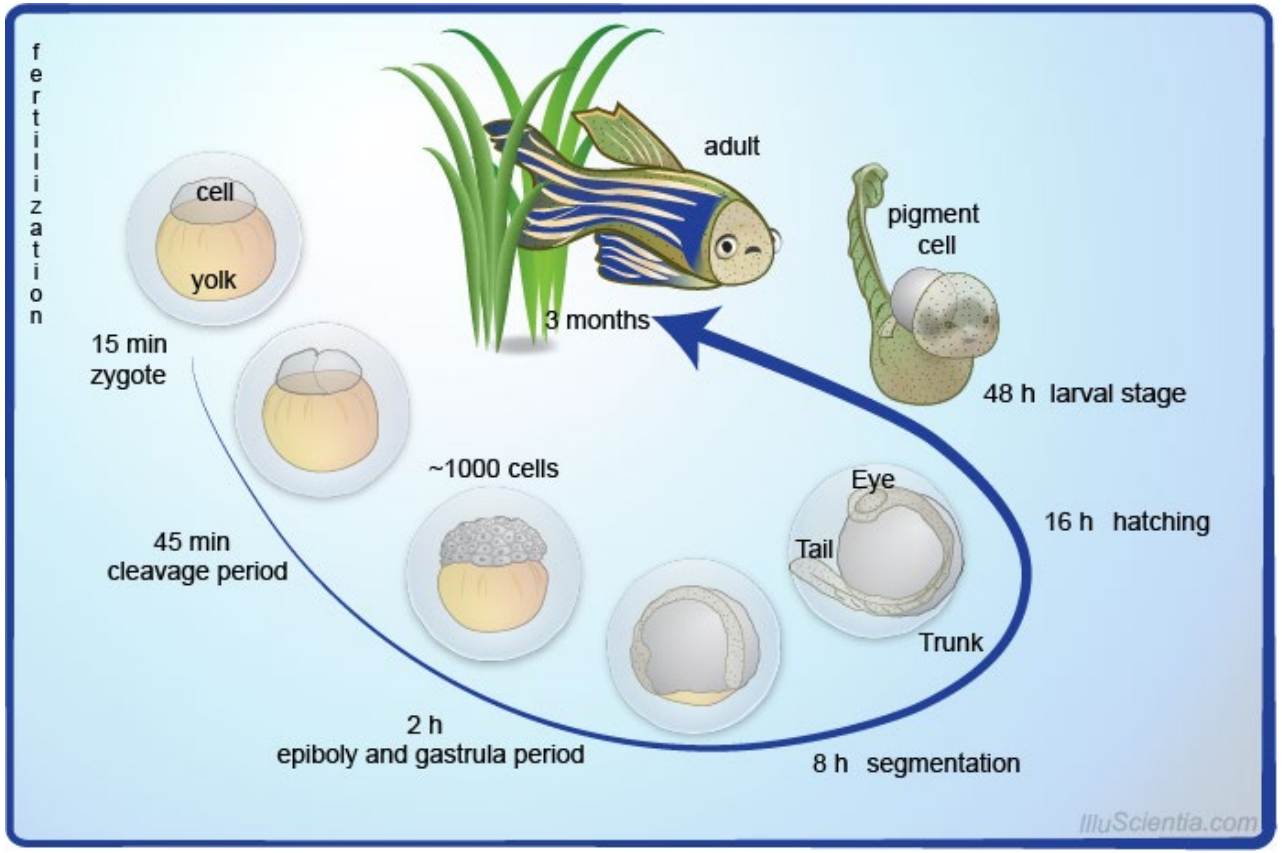
Danio rerio (zebrafish)

Drosophila melanogaster (fruit fly)

Daphnia (water flea)

C. elegans (round worm)

- Integrated model
- Ease of genetic manipulation
- Drug screening
- Reproductive and Developmental Toxicity



In Vitro Assays in Practice

- Valuable for chemical safety and risk assessment
  - Routinely used by industries and regulatory authorities
  - OECD
    - Skin Irritation
    - Serious Eye Damage/Eye Irritation
    - Sensitization
    - Genotoxicity

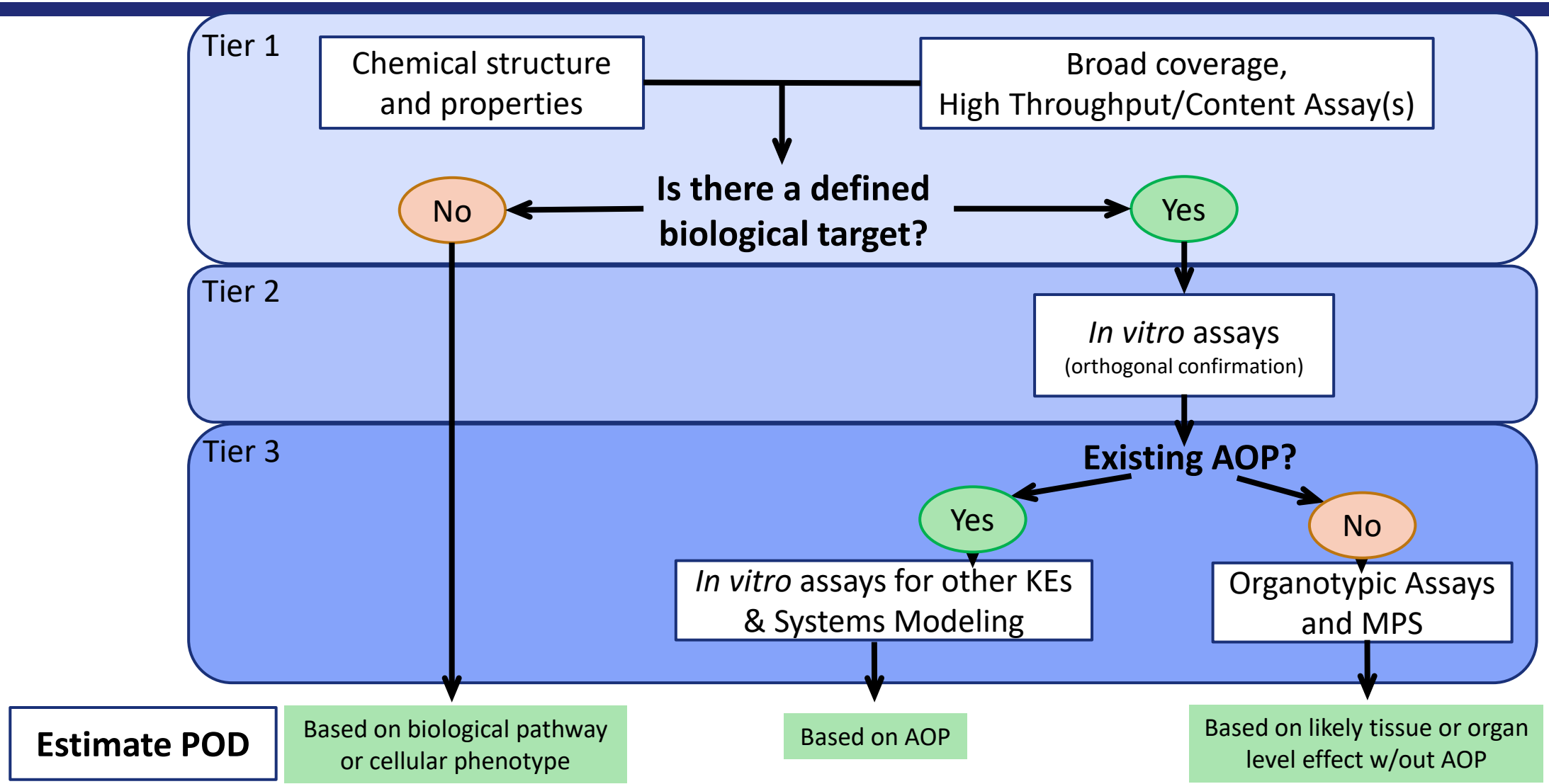
  } Can replace some traditional *in vivo* animal tests

- Potential replacement for uncertainty factors
- Limitations
  - Metabolism *in vitro*
  - Non-specific binding to plastics in *in vitro* system
  - Uncertainty analysis*
- Need analysis pipeline and integration approaches
- Need international involvement and case studies

*same with animal studies

https://ntp.niehs.nih.gov/whatwestudy/niceatm/accept-methods/index.html ;
https://echa.europa.eu/documents/10162/21650280/oecd_test_guidelines_skin_sensitisation_en.pdf

Example of a Tiered Hazard Evaluation Approach

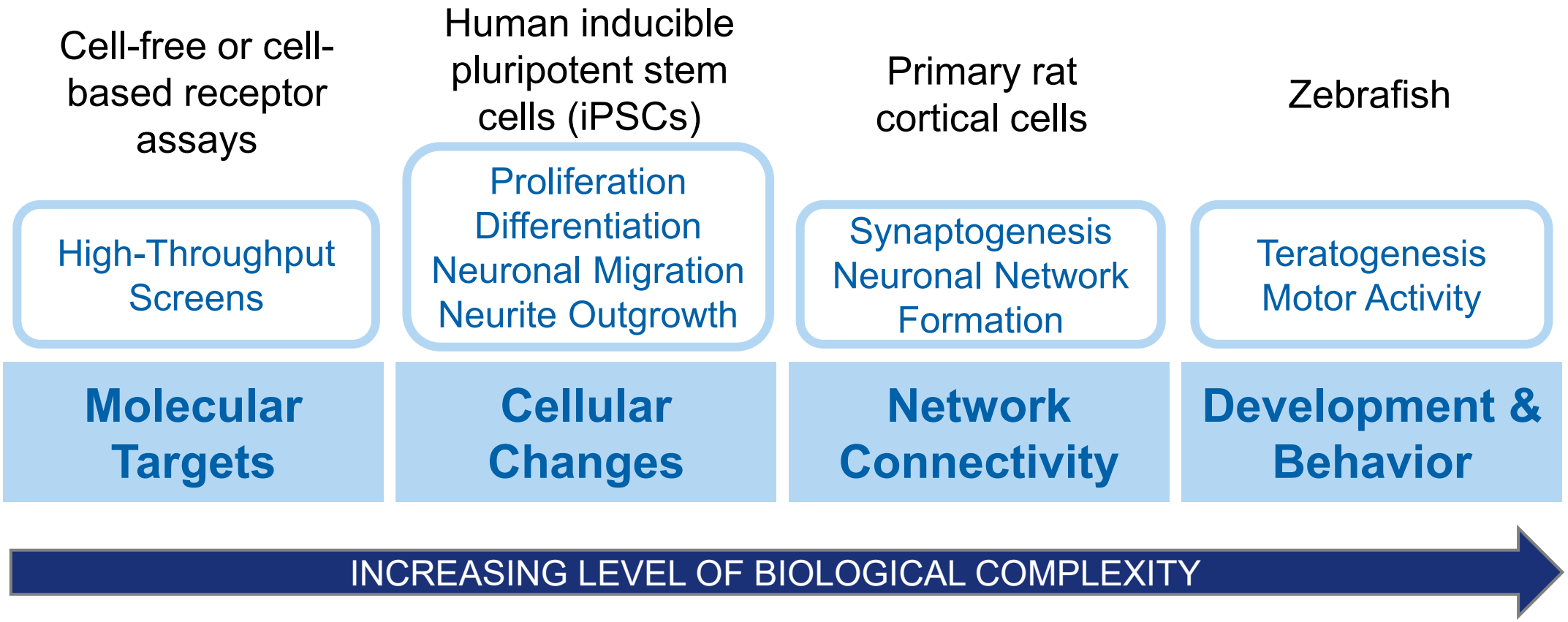


Thomas RS, et al. Toxicol Sci. 2019 Jun 1;169(2):317-332. doi: 10.1093/toxsci/kfz058.

thought exercise

Can You Imagine a Way to Integrate *In Vitro* Assays into Your Own Assessments? What about for Developmental Neurotoxicity (DNT)?

- No standard regulatory data requirements for DNT
- Resource intensive, difficult to interpret
- ~100–150 chemicals with DNT toxicological hazard information
- We know pathways for neurodevelopment



International Effort to Improve DNT Testing

- International Collaboration (e.g., EFSA, OECD, US EPA)
- OECD DNT Expert Group
  - Improve DNT testing
  - Incorporate mechanistic knowledge
  - Provide regulatory relevant examples through case studies
  - Accelerate regulatory uptake of the DNT *in vitro* battery

EFSA—European Food Safety Authority

OECD—The Organisation for Economic Co-operation and Development

1. Adverse outcome pathways (AOPs)
2. *In vitro* battery
3. OECD Integrated Approaches to Testing and Assessment (IATA)

Sachana M, Shafer TJ, Terron A. Biology (Basel). 2021 Jan 23;10(2):86. doi: 10.3390/biology10020086.
Aschner M, et al. ALTEX. 2017;34(1):49-74. doi:10.14573/altex.1604201. Epub 2016 Jul 25

International Discussion to Increase NAM Use

OECD Integrating Approaches to Testing and Assessment (IATA)

"IATA are pragmatic, science-based approaches for chemical hazard characterisation that rely on an integrated analysis of existing information coupled with the generation of new information using testing strategies."

http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm

Case studies are critical to acceptance

Problem formulation
- Define the regulatory need
- Identify relevant information

Gather and evaluate existing data
- *In vivo*, *in vitro*, *in silico*

Weight of Evidence
- Characterize ertainty
- ce, consider additional info
- ds
- al methods

Endocrine-Disrupting Chemicals (EDC)

Adapted from OECD

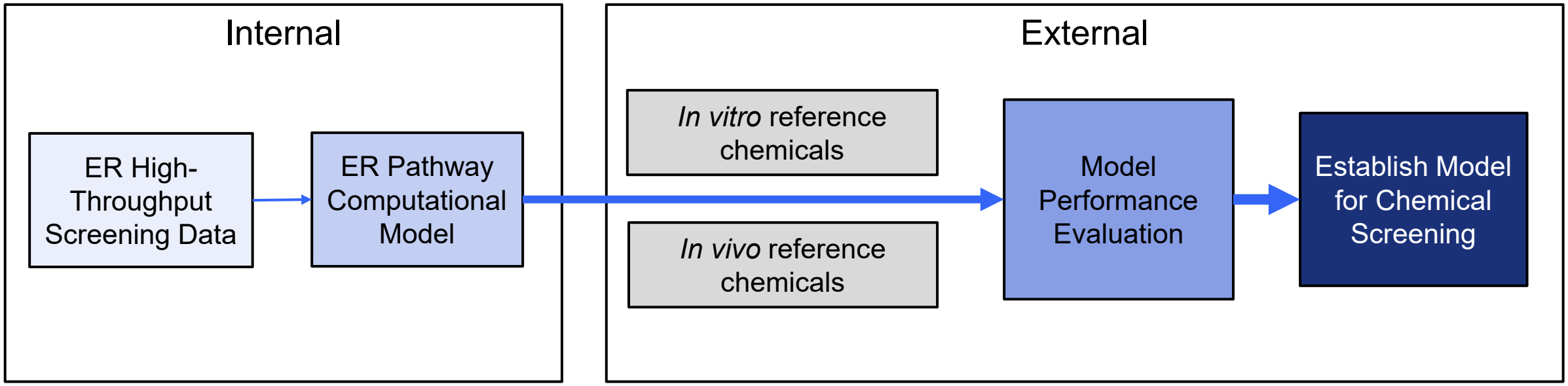
http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2020)25&docLanguage=en ;
http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm

Endocrine-Disrupting Chemicals (EDCs)

- EDCs are a diverse set of substances that have the potential to interfere with normal endocrine function and lead to an adverse outcome
- Regulatory agencies in many countries evaluate endocrine activity of environmental chemicals for specific regulatory endpoints
- US EPA Endocrine Disruptor Screening Program (EDSP) uses a two-tiered testing battery approach
  - Tier 1 screens for potential to interact with estrogen, androgen, or thyroid hormone
    - Running Tier 1 battery costs ~$1 million / chemical
    - Tier 1 tests on 52 chemicals over 6 years, ~10,000 chemicals on EDSP Universe list

    } Need for alternative approaches
  - Tier 2 tests to verify the interaction and quantify dose-response relationship
- IATA EDC Case Study
  - Identification of endocrine disruption via estrogen receptor agonism by a substance

Overall Approach



Adverse Outcome Pathway (AOP) for EDCs

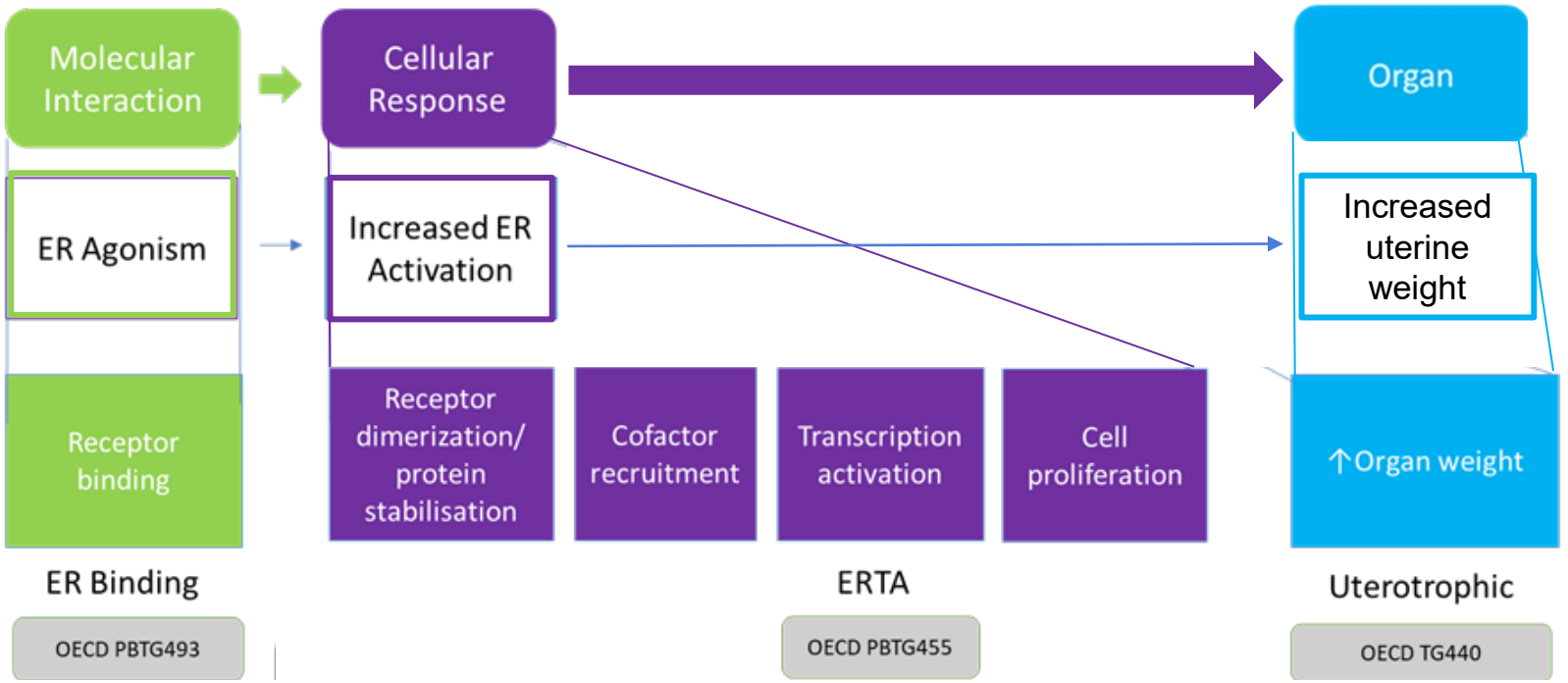
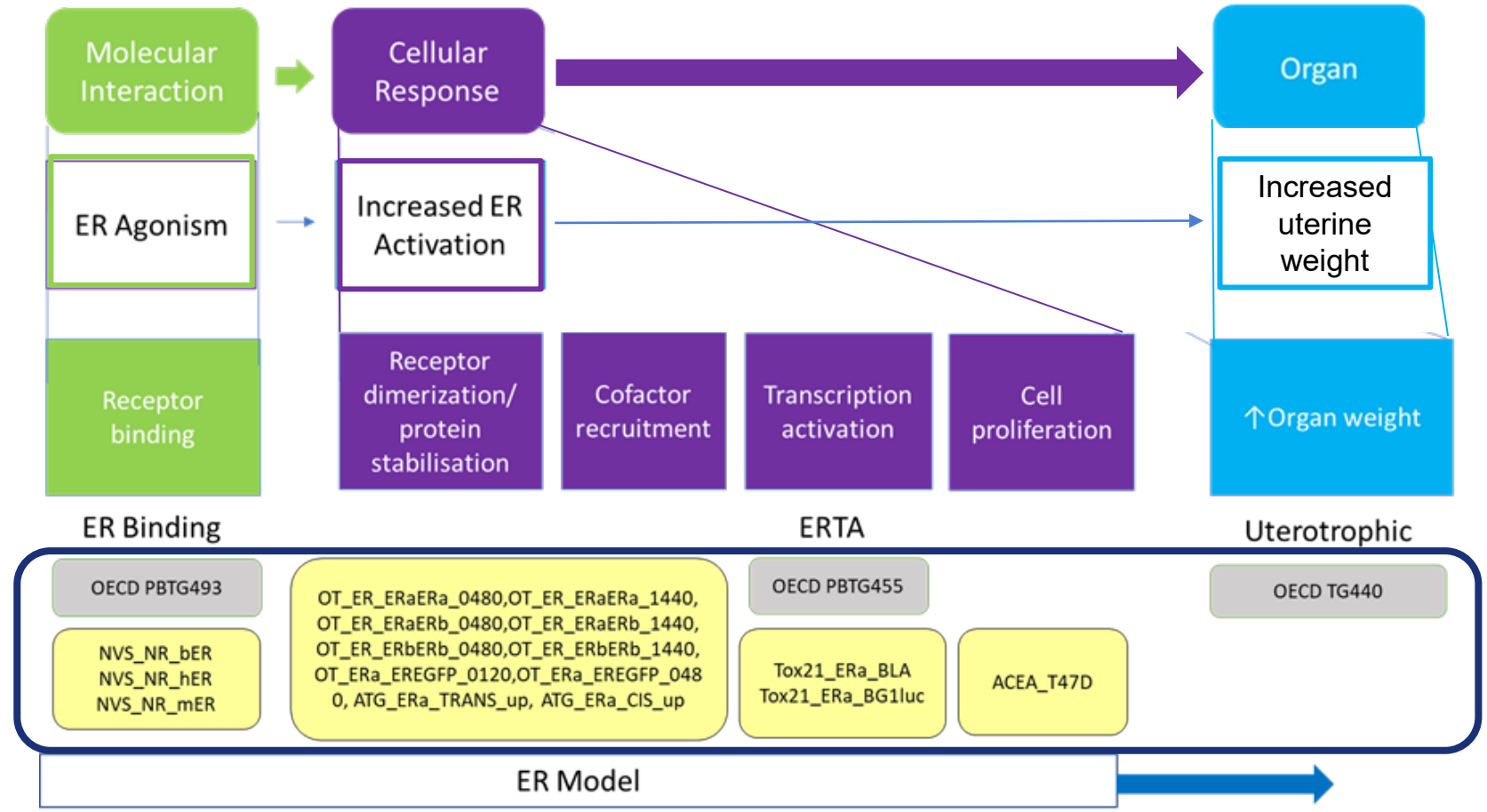


Image used with author permission and adapted from Browne P, Noyes PD, Casey WM, Dix DJ. Environ Health Perspect. 2017 Sep 1;125(9):096001. doi: 10.1289/EHP1304.

Adverse Outcome Pathway (AOP) for EDCs



Specific *in vitro* assays

Image used with author permission and adapted from Browne P, Noyes PD, Casey WM, Dix DJ. Environ Health Perspect. 2017 Sep 1;125(9):096001. doi: 10.1289/EHP1304.

ER Model from *In Silico* Aggregation of HTS Assays

- Orthogonal assays on pathway
  - Different technologies
  - Different points in pathway
- No assay is perfect
  - Assay interference
  - Noise
- Use computational model to integrate assays
- Model creates a composite dose-response curve for each chemical to summarize results from all assays
- Evaluate model against reference chemicals

Judson RS, et. al. (2015) Toxicol Sci

Evaluation Using *In Vitro* & *In Vivo* Reference Chemicals

In vitro

- OECD Test Guideline 457 BG1 ER Transactivation Guidance document: https://doi.org/10.1787/9789264185395-en

Model Performance 40 chemicals
Accuracy: 93% (95%)
Sensitivity: 93% (93%)
Specificity: 92% (100%)

*Values in parentheses exclude chemicals w/inconclusive model scores

In vivo

- Comprehensive literature search identified 103 chemicals; however…
  - **Uncertainty in *in vivo* guideline data**
  - 26% of chemicals tested multiple times in the uterotrophic assay gave discrepant results

Model Performance 43 chemicals
Accuracy: 86% (95%)
Sensitivity: 97% (97%)
Specificity: 67% (89%)

*Values in parentheses exclude chemicals w/inconclusive model scores

Browne P et al (2015) EHP ; Judson RS, et. al. (2015) Toxicol Sci
Kleinstreuer et al. EHP 2016 ; Browne et al. ES&T (2015)

Outcome: Risk Assessment Guidance

EPA notice: "The approach incorporates validated high throughput assays and a computational model and, based on current research, can serve as an alternative for some of the current assays in the Endocrine Disruptor Screening Program (EDSP) Tier 1 battery."

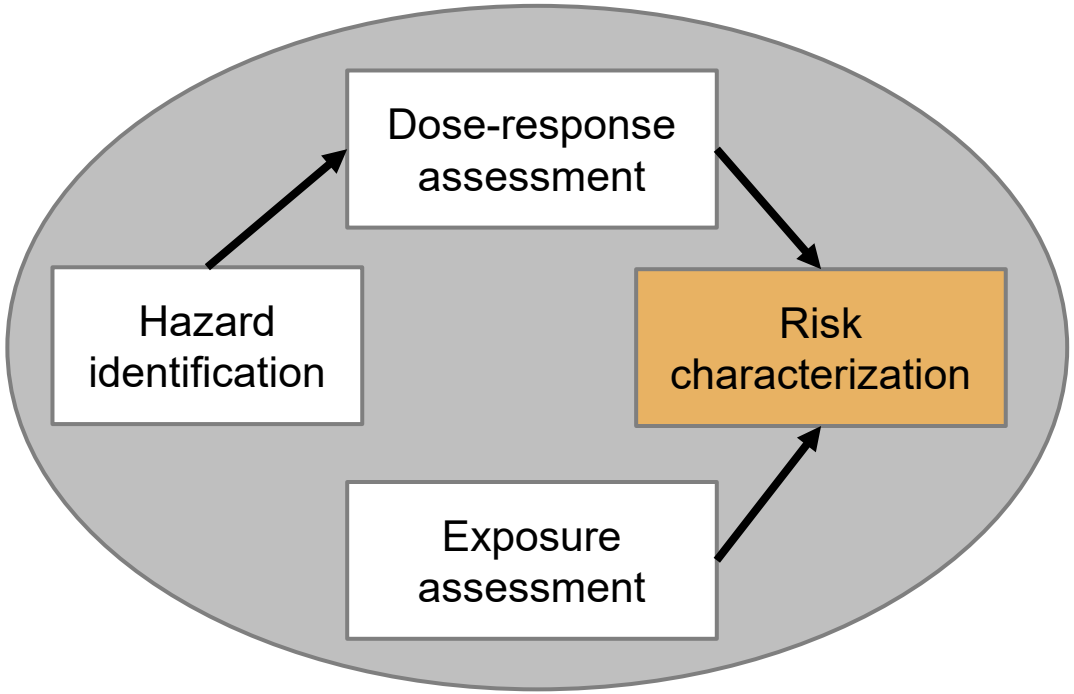
US Environmental Protection Agency (2015) National Archives Federal Register PA-HQ-OPPT-2015-0305

OECD:

- Integrated Approach for Testing Assessment (IATA) for the ER assays was reviewed and published
- Assays incorporated in an annex of Test No. 455, covering all ER transcriptional assays
  - Test Guidelines give more specific details on how to run each assay and combine the results and will take multiple years for full guideline to be made

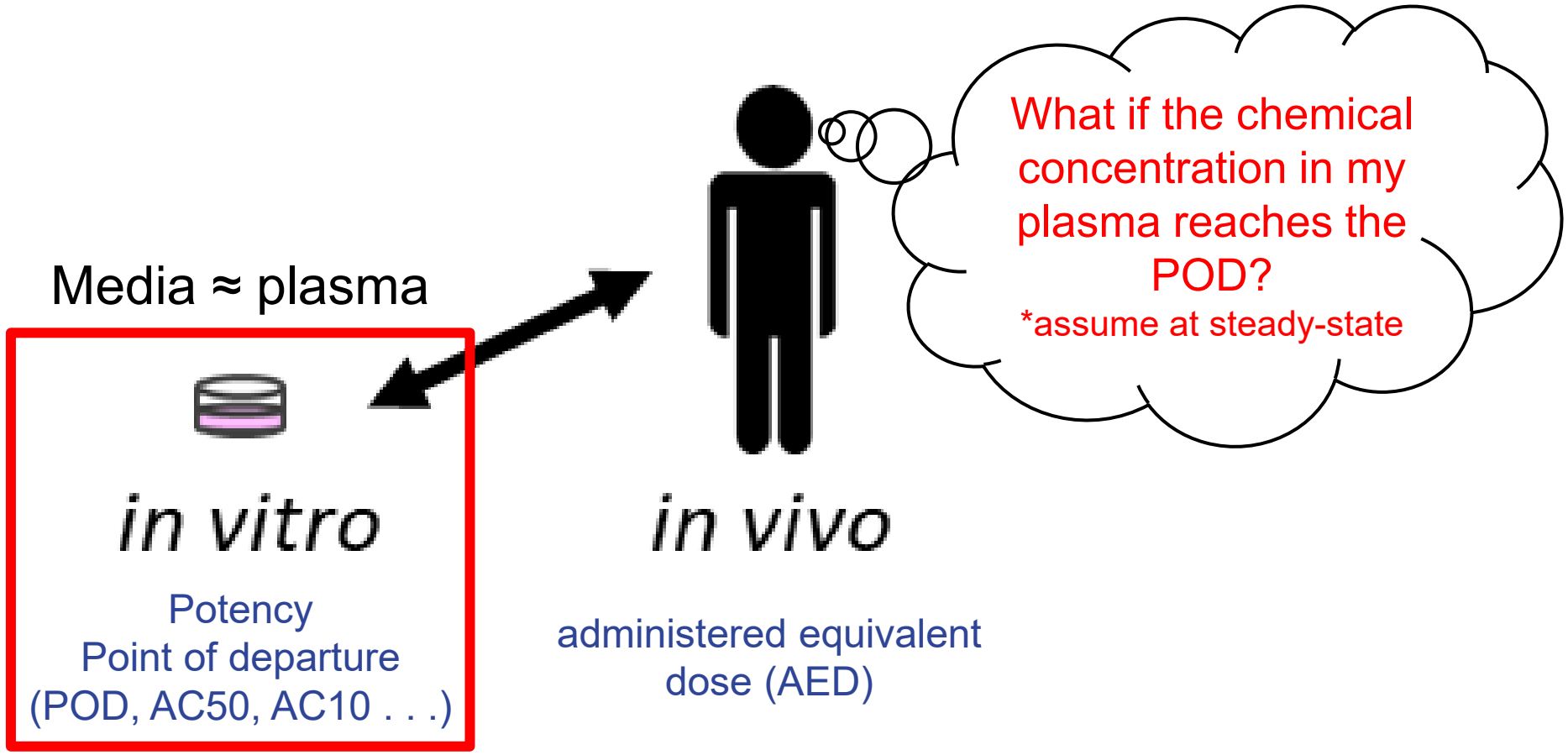
Webster F, et. al. (2019) Regul Toxicol Pharmacol ; OECD (2015) Test No. 455 https://doi.org/10.1787/9789264243040-en

How Can We Use Alternative Approaches in Risk Characterization?



1. *In silico* read-across (data gap analysis)
2. Hazard assessment (ID and dose-response)
   a. *In vitro* assays
   b. Making sense of *in vitro* potencies using *in vitro* to *in vivo* extrapolation (IVIVE)
3. High throughput exposure assessment
4. Risk characterization

Making Sense of *In Vitro* Potencies



Tan YM et al. 2007; Wetmore BA et al. 2015

In Vitro-In Vivo Extrapolation (IVIVE)

aka reverse dosimetry, reverse toxicokinetics

Toxicokinetics + Toxicodyanmics

Definition: utilization of *in vitro* experimental data to predict phenomena *in vivo*

Use of IVIVE tools to incorporate dosimetry has enabled a shift from a hazard-based to a risk-based interpretation of *in vitro* data

input

$$\approx \quad C_{ss} = \frac{\text{oral dose rate}}{(\text{GFR} * \text{F}_{ub}) + \left(\text{Q}_1 * \text{F}_{ub} * \frac{Cl_{int}}{\text{Q}_1 + \text{F}_{ub} * Cl_{int}} \right)}$$

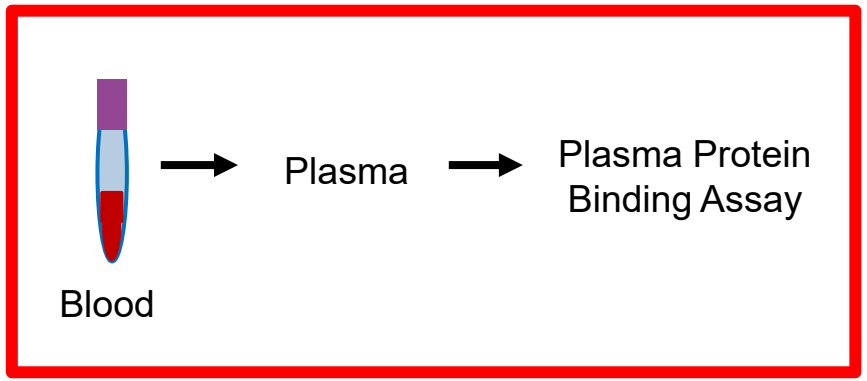
kidney *liver*

100% oral bioavailability assumed; kinetics are assumed to be linear

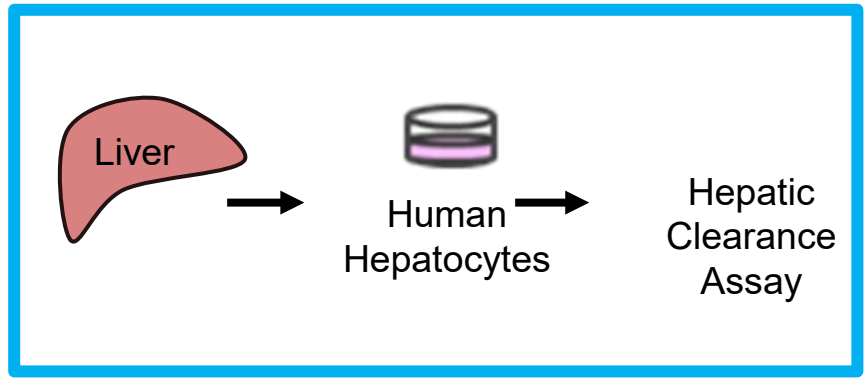
RG Wilkinson and DG Shand, 1975; BA Wetmore, et. al., 2012

Estimating Clearance Using *In Vitro* Measurements of Fub & Clint

Fraction of the compound unbound in plasma



Intrinsic metabolic clearance



$$C_{ss} = \frac{\text{oral dose rate}}{\left(GFR * F_{ub}\right) + \left(Q_1 * F_{ub} * \frac{Cl_{int}}{Q_1 + F_{ub} * Cl_{int}}\right)}$$

kidney *liver*

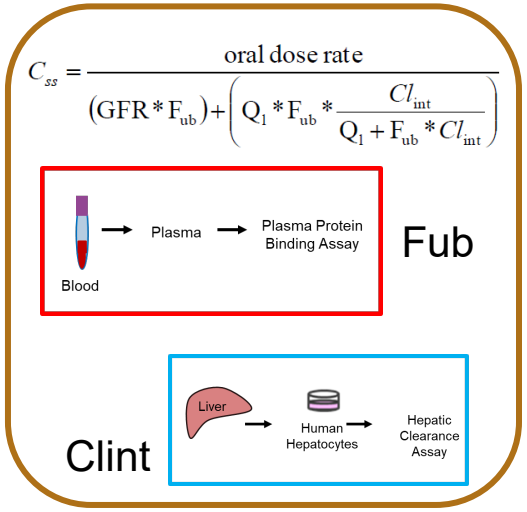
Further efforts have focused on predicting Fub & Clint using *in silico* approaches

RG Wilkinson and DG Shand, 1975; BA Wetmore, et. al., 2012

High-Throughput Toxicokinetics (HTTK)

Meanings of "HTTK"

- Any component of evaluating toxicokinetics in a high-throughput manner
  - E.g., *in vitro* or *in silico* Clint and/or Fup
  - E.g., Css
- HTTK R-package
  - Generic pharmacologically based toxicokinetic (PBTK) model
  - Developed at the US EPA, free and publicly available
  - High throughput with appropriate input data
  - Forward dosimetry
  - Reverse dosimetry/reverse toxicokinetics (IVIVE)

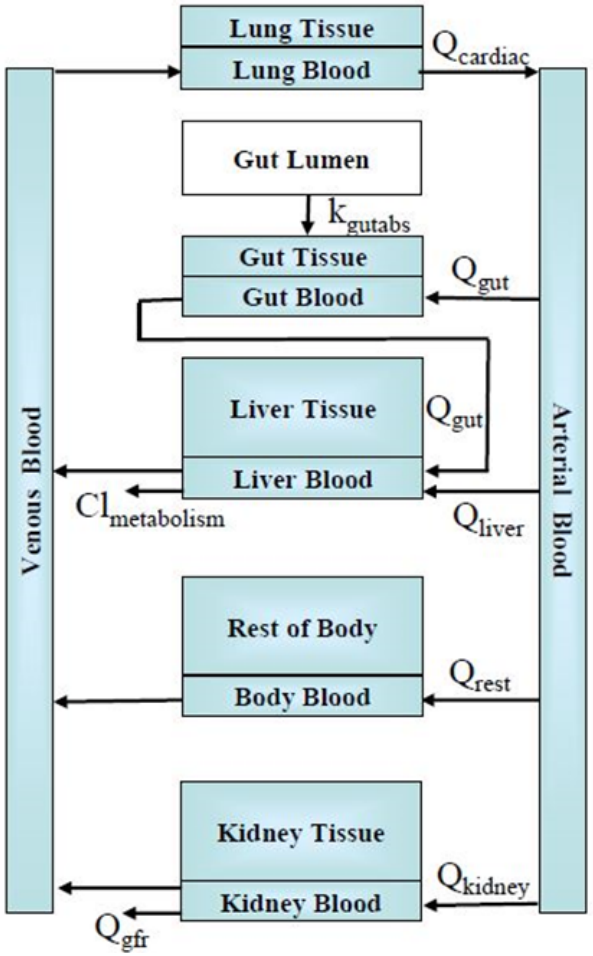


Commercial PBTK Software

- Simcyp: https://www.certara.com/
- ADMET Predictor / GastroPlus: https://www.simulations-plus.com/
- MEGen: http://cefic-lri.org/toolbox/pbpkmegen/
- IndusChemFate: http://cefic-lri.org/toolbox/induschemfate/

High-Throughput Toxicokinetics (HTTK) R-package

Generic PBTK model



- Simple models (1 and 3 compartments)
- Generic PBTK model
- Specialty: gas inhalation, aerosol inhalation, dermal, human gestational model

Body is represented by "compartments" and connected by "flows," mass balance applies. Some compartments represent individual organs/tissues (e.g., liver); others are "lumped" (e.g., rest of body).

Parameterized using physicochemical properties (QSARs) + Fup & Clint data

- >1,000 and >8,000 chemicals with *in vitro* or *in silico* estimated parameter data, respectively

Various species (e.g., rat, rabbit, dog, human, monkey)

Assumptions

- Fast absorption rate (1/h)
- 100% bioavailability
- Chemical exits via metabolism or excretion by glomerular filtration

Image used with author permission from: Pearce RG, Setzer RW, Strope CL, et al. httk: R Package for High-Throughput Toxicokinetics. J Stat Softw. 2017;79(4):1-26

HTTK-Pop: Population Simulator for HTTK R-package

Not every adult is the same. Not every person is an "average" adult (e.g., children, elderly). *In vitro* and *in silico* tools to predict TK variability.

Similar approach to many commercial software

Sample NHANES quantities

Sex
Race/ethnicity
Age
Height
Weight
Serum creatinine

Regression equations from literature (+ residual marginal variability)

Predict physiological quantities

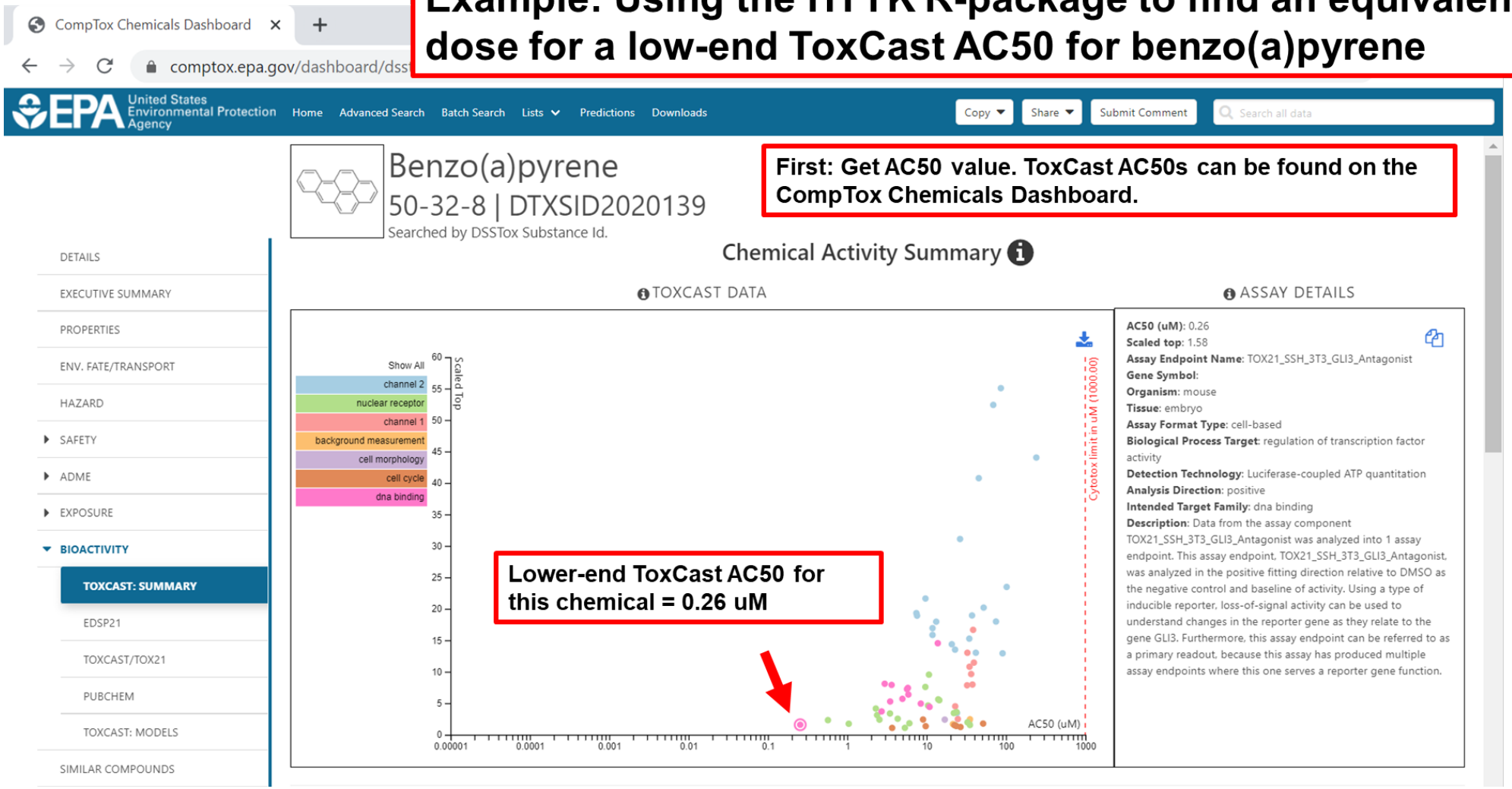
Tissue masses
Tissue blood flows
GFR (kidney function)
Hepatocellularity

Potentially eliminate the need for some uncertainty factors—human heterogeneity in vulnerability to exposures

Adapted from https://ntp.niehs.nih.gov/iccvam/meetings/ivive-wksp-2016/wksp-ppts/1-2-ring-508.pdf

How Can I Calculate Equivalent Dose from In Vitro Data?

Example: Using the HTTK R-package to find an equivalent dose for a low-end ToxCast AC50 for benzo(a)pyrene



Calculating equivalent dose is straight-forward

Use HTTK R-package Function calc_mc_oral_equiv()

```
> #Steady-state equivalent dose (mg/kg BW/day) to produce 0.26 uM in plasma:
> library(httk)
> set.seed(42)
> calc_mc_oral_equiv(conc=0.26,
                     chem.name="benzo(a)pyrene",
                     which.quantile = c(0.95, 0.5, 0.05),
                     input.units = "uM",
                     output.units = "mgpkgpday")
uM concentration converted to mgpkgpday dose for 0.95 0.5 0.05 quantile.
      95%       50%        5%
0.003821 0.019090 0.067080
```

input

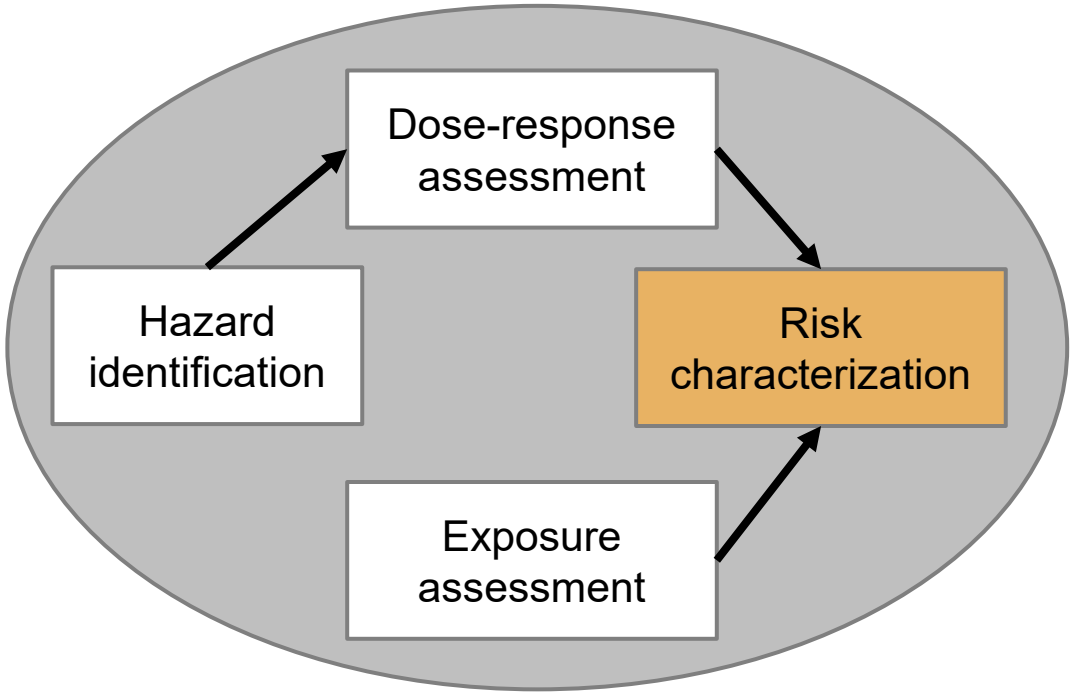
output

In Vitro to *In Vivo* Extrapolation in Practice

- Provide context for *in vitro* data with respect to *in vivo* interaction likelihood
  - Conservative estimate (e.g., 100% assumed bioavailable)
  - Species differences
  - Population variability
    - Identifying sensitive population
    - Replace use of default safety factors in risk assessment

- Challenges
  - Chemical training sets with PK data
  - Phase II and III metabolism (transporters, glucuronidation)
  - Tissue distribution (blood versus target tissue)
  - Css versus Cmax

How Can We Use Alternative Approaches in Risk Characterization?



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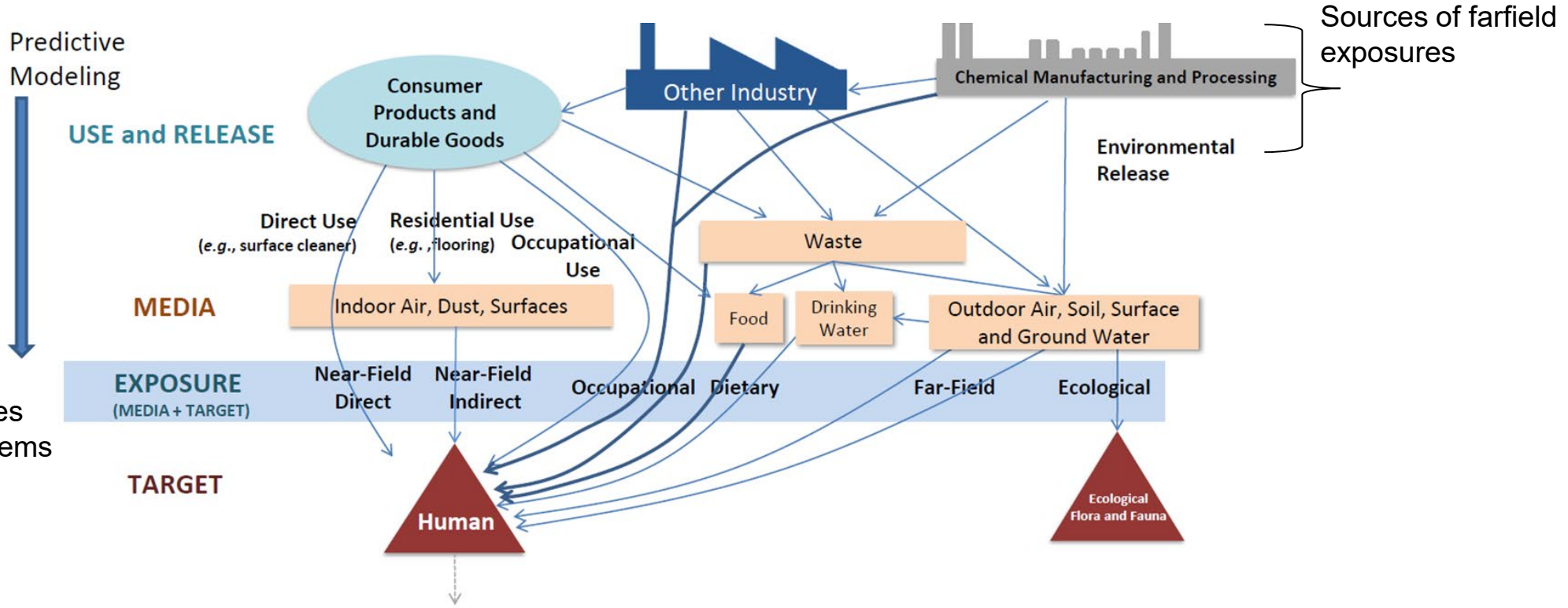
Rapid Exposure Predictions (ExpoCast)

https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research

- High-throughput, rapid exposure predictions for thousands of chemicals
- Environmental chemical focused
- Multiple routes of exposure

We can try to predict the exposure by describing the process leading to exposure



Nearfield exposures can be daily use items

Image used with permission from John Wambaugh and Kristin Isaacs

Wambaugh et al. "New Approach Methodologies for exposure science", Current Opinions in Toxicology, 15, 76-92 (2019)

Farfield Exposure Models

https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research

- Predict exposure from chemicals that are released into the outdoor environment (air, water, soil) through industrial releases

- USETox
  - https://usetox.org/
  - Treat models like related assays and look for consensus while considering model appropriateness
  - Global scientific consensus fate, exposure, and effect model

- Risk Assessment IDentification and Ranking (RAIDAR) Model
  - https://arnotresearch.com/raidar/
  - Environmental fate and transport mass balance model linked with food web bioaccumulation models for representative ecological and agricultural targets
  - Applicable when little or no empirical data exist. Can “bin” chemicals into high or low risk potential.

Arnot, J.A.; Mackay D. 2008. Environ. Sci. Technol. ; Arnot, J.A.; Mackay, D.; Webster, E.; Southwood, J. 2006. Environ. Sci. Technol.

Nearfield Exposure Models

https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research

- Provide estimates of exposure (over various product types, scenarios, and routes) to chemicals used in consumer products and in-home products

- Stochastic Human Exposure and Dose Simulation Model (SHEDS)
  - Probabilistic models that can estimate everyday exposures
  - Detailed use patterns drive exposure
  - Multiple models: multimedia, dietary, residential, high-throughput

    Isaacs KK, et al. Environ Sci Technol. 2014 Nov 4;48(21):12750-9.

- EPA Chemical and Products Database (CPDat)
  - >75,000 chemicals and 15,000 consumer products

Williams, P., B. Hubbell, E. Weber, C. Fehrenbacher, David Hrdý and V. Zartarian. “CHAPTER 3 An Overview of Exposure Assessment Models Used by the US Environmental Protection Agency.” (2009).

Dionisio, K., et al. Sci Data 5, 180125 (2018).

Calibration and Evaluation of Models

https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research

- Systematic Empirical Evaluation of Models (SEEM) framework
  - Calibration and evaluation of models toward consensus predictions
  - Compare with National Health and Nutrition Examination Study (NHANES)—blood and urine

Wambaugh et al. “New Approach Methodologies for exposure science,” Current Opinions in Toxicology, 15, 76-92 (2019)

Non-targeted Chemical Screening

https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research

- Identify unknown chemicals in water, soil, and other types of samples, without having a preconceived idea of what chemicals are present

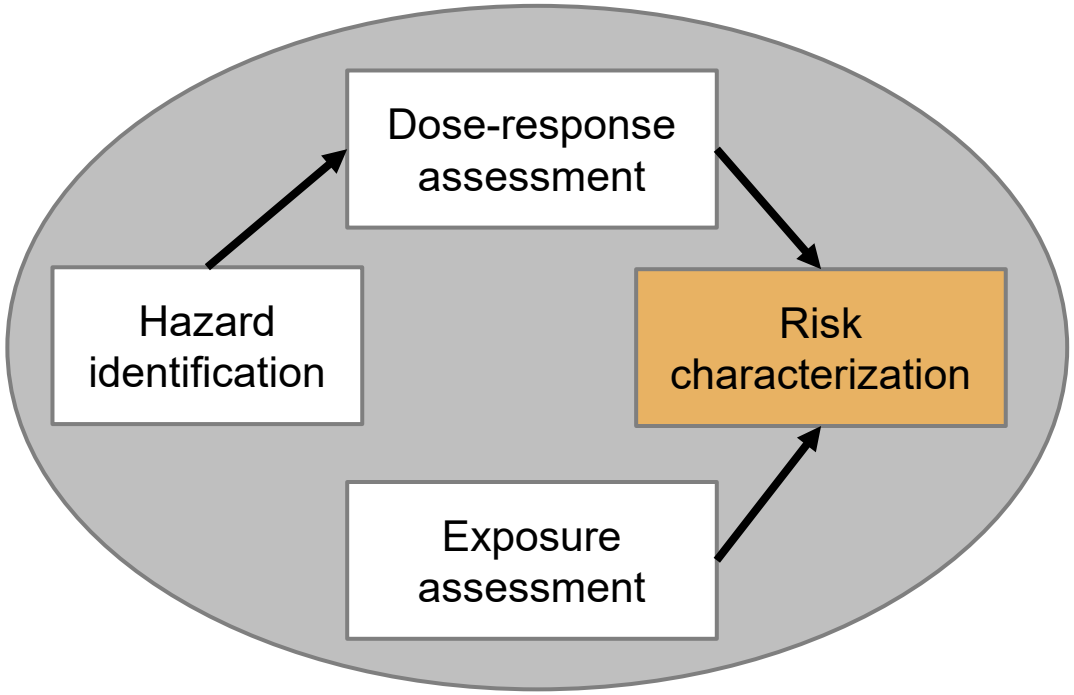
- Non-Targeted Analysis Collaborative Trial (ENTACT)
  - Evaluate ability of non-targeted methods to consistently and correctly identify unknown chemicals in a sample
  - 30 academic, government, and industry groups

- E.g., detection of GenX in the Cape Fear River, NC

Newton, S.R., *et al. Anal Bioanal Chem* (2020). https://doi.org/10.1007/s00216-020-02658-w

https://www.northcarolinahealthnews.org/2017/10/18/local-scientists-uncovered-cape-fear-river-genx-saga/

How Can We Use Alternative Approaches in Risk Characterization?



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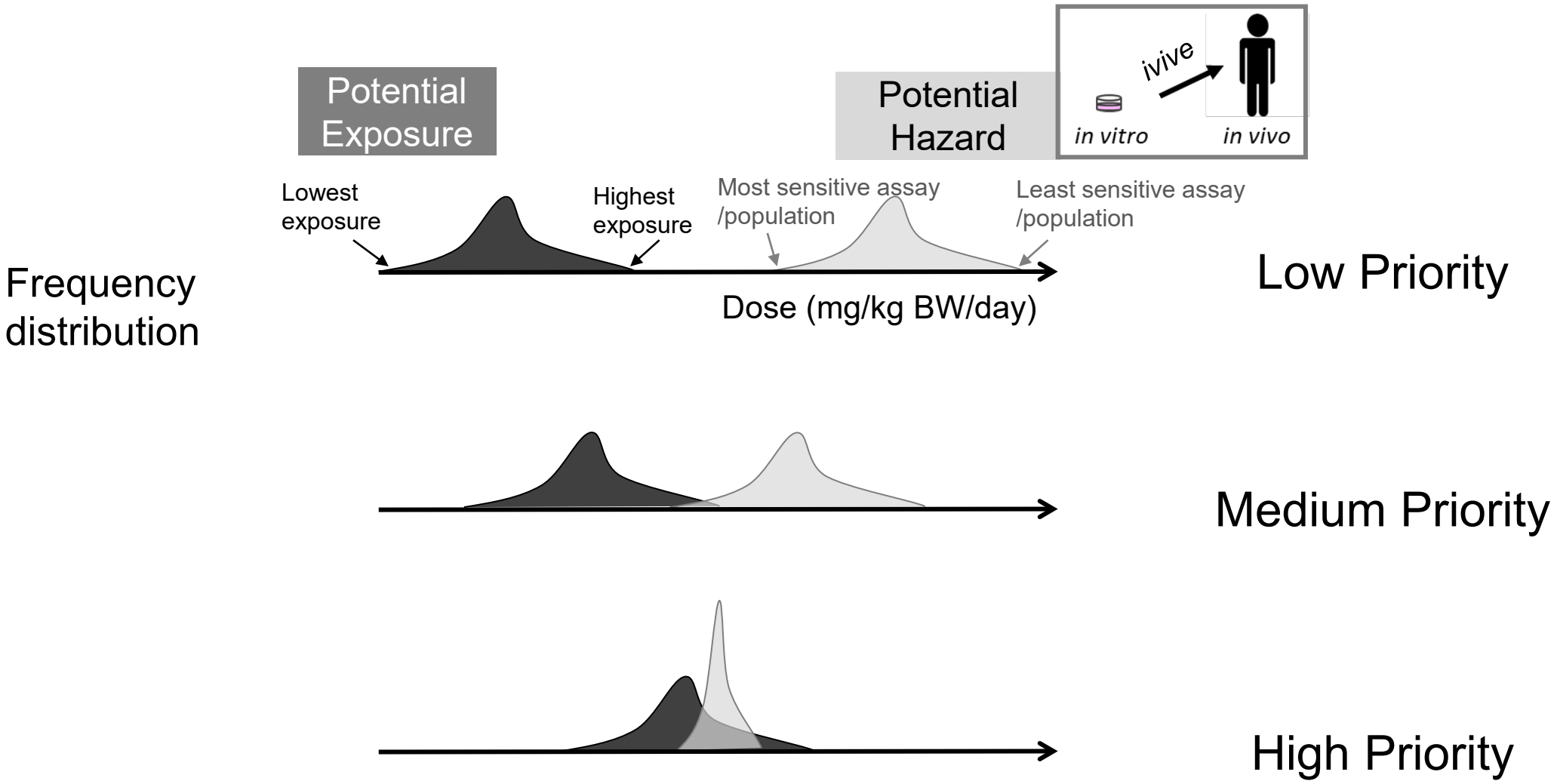
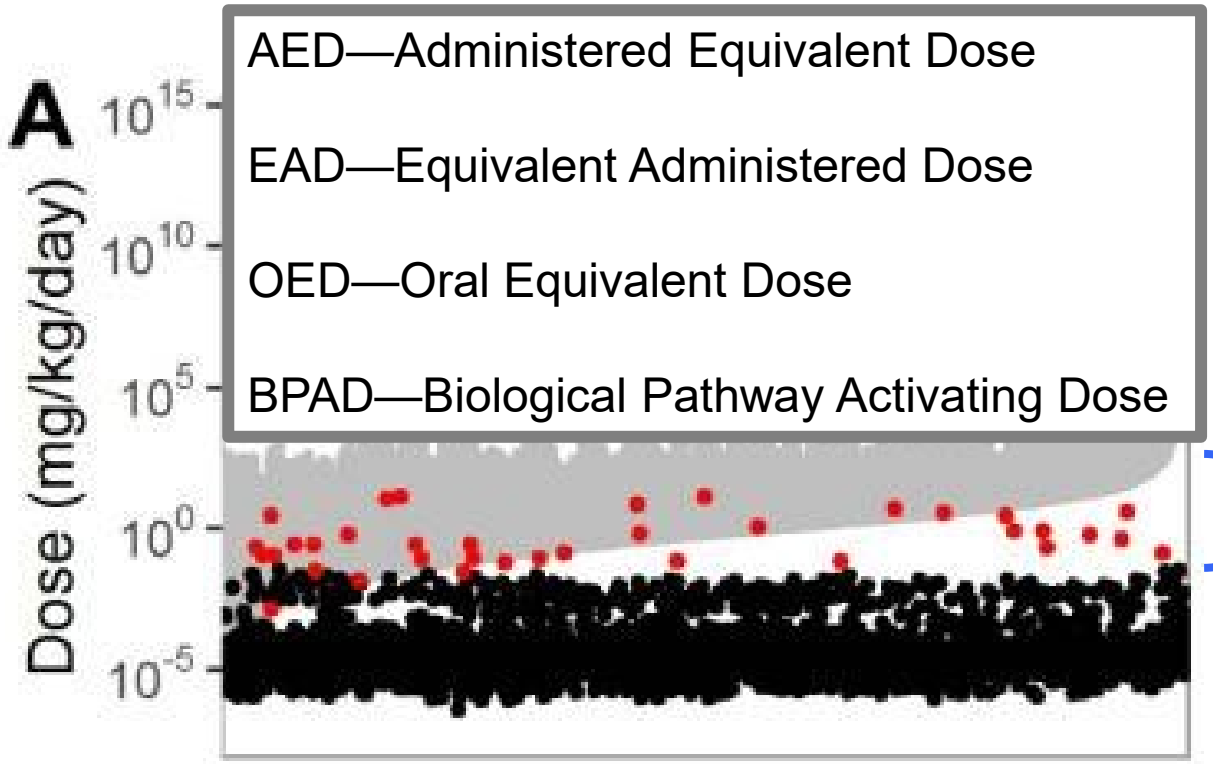
Bringing It All Together: High-Throughput Risk-Based Prioritization



Enabling Risk Based Prioritization

Margin of Exposure (MOE)



Equivalent Dose
(ToxCast + HTTK)

Margin of Exposure (MOE)

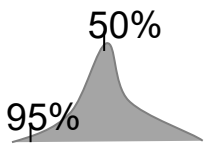
ExpoCast

ToxCast chemicals (limited by availability of Fup & Clint data)

Enabling Risk Based Prioritization—Alternative View

BER: Bioactivity-Exposure Ratio (also known as AER: Activity-Exposure Ratio)

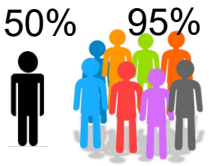
Administered Equivalent Dose (AED)



Assay POD

- Sensitive (95%)
- Sensitive (95%)
- Average (50%)
- Average (50%)

+



Exposure (IVIVE)

- Average (50%)
- Sensitive (95%)
- Average (50%)
- Sensitive (95%)

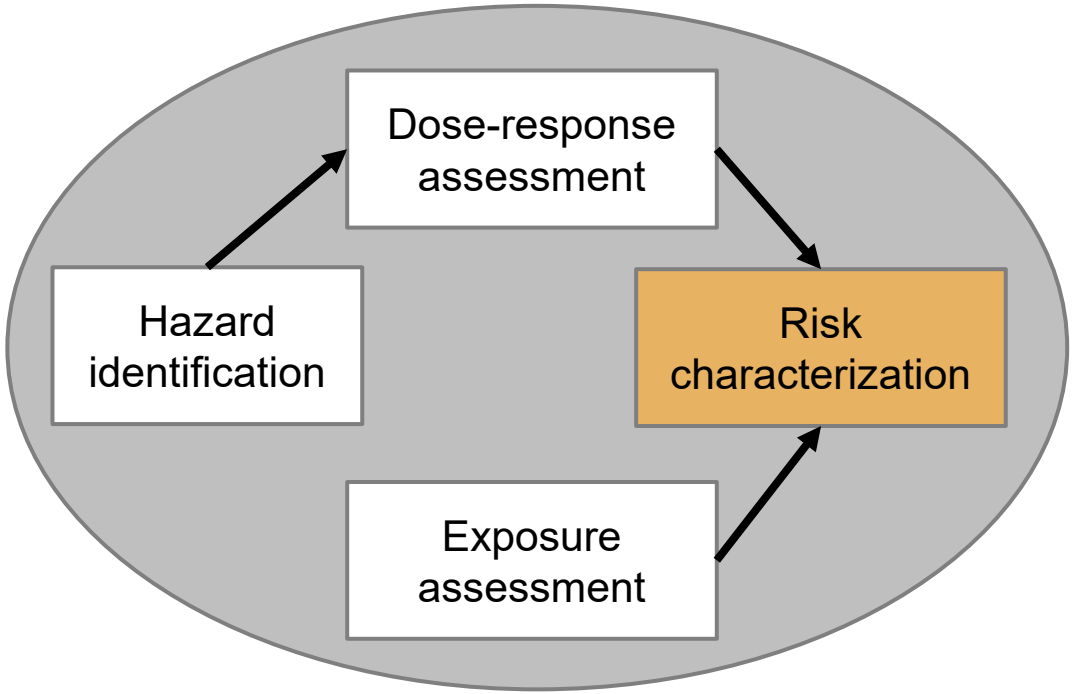
Compare to Predicted Exposure (e.g., ExpoCast)

Make choices based on tolerable uncertainty (i.e., on use case)

Paul Friedman K, et al. Toxicol Sci. 2020 Jan 1;173(1):202-225.

thought exercise

How Can We Use Alternative Approaches in Risk Characterization?



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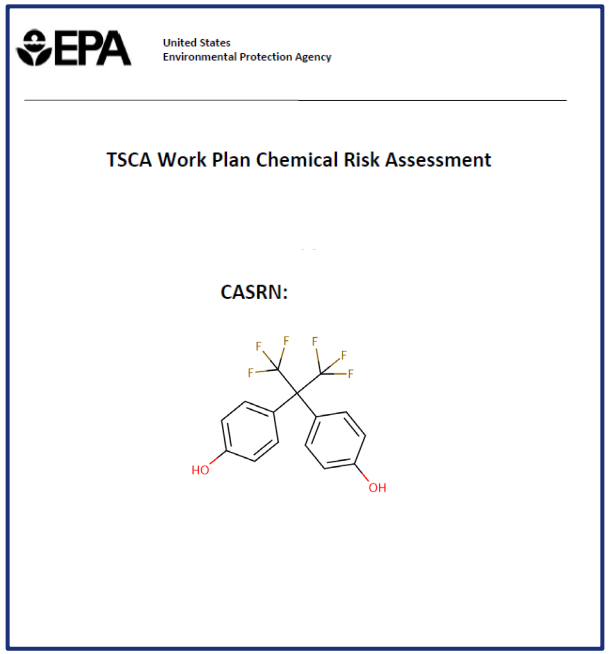
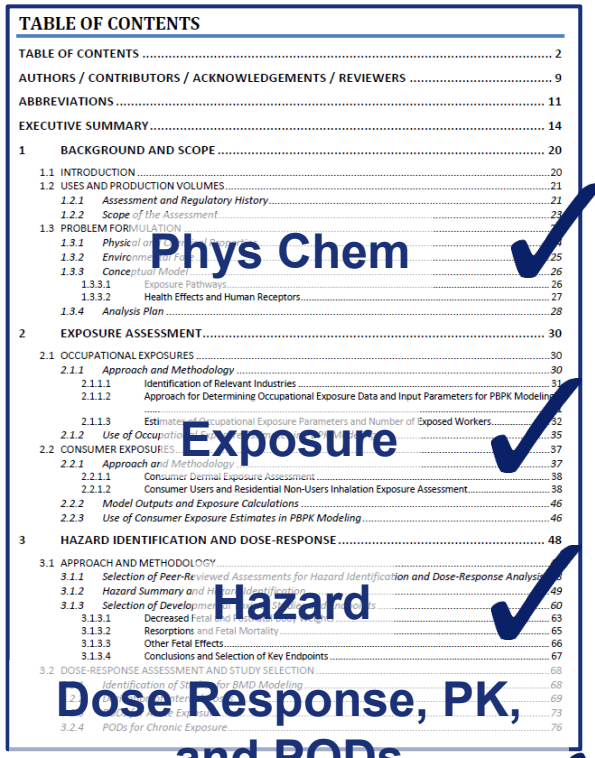
The basics were shown throughout this presentation

Covering All the Components of a 21st-Century Risk Assessment


EPA United States Environmental Protection Agency

TSCA Work Plan Chemical Risk Assessment

CASRN: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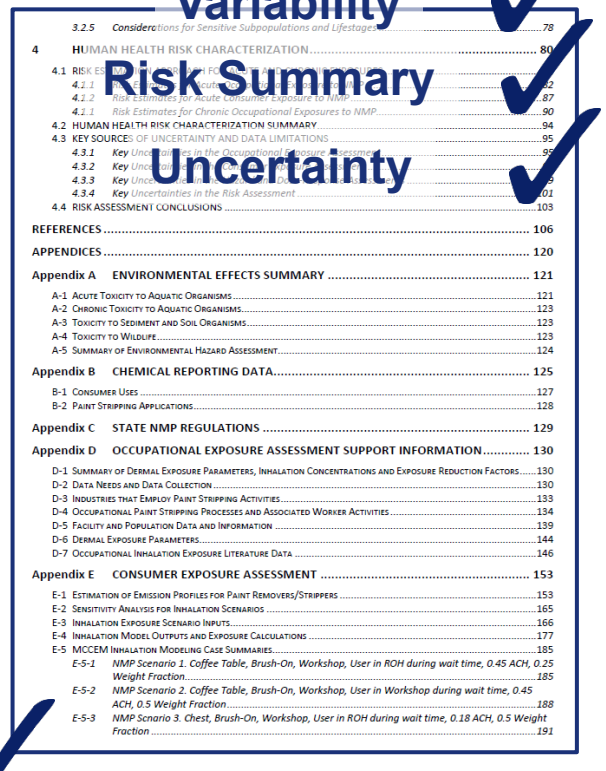


Phys Chem ✓

Exposure ✓

Hazard ✓

Dose Response, PK, and PODs ✓

Variability ✓

Risk Summary ✓

Uncertainty ✓

Closing

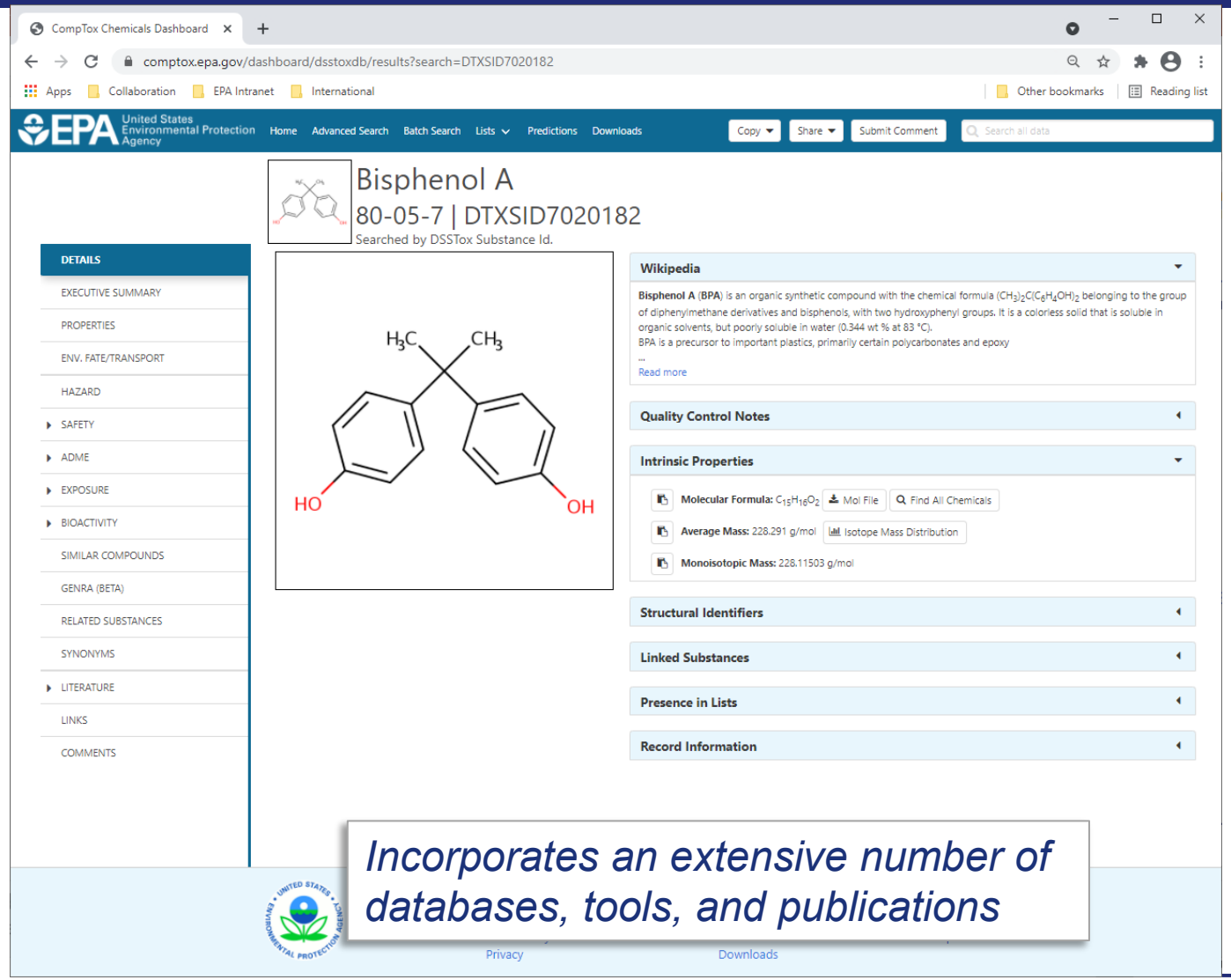
- Incorporating new technologies and innovations through computational toxicology can more rapidly and inexpensively screen chemicals for potential adverse biological effects.
- The field has made great advances in the development of NAMs and tools for filling information gaps for decision-making and integrating those tools and data streams into chemical risk assessment.
- International collaborations are leveraging resources and developing NAMs that can support different regulatory contexts.
- Building confidence in the use of NAMs for regulatory decision-making is key to the increased implementation of these methods.

What Is Needed to Expand Translation and Implementation of Computational Toxicology Approaches?

- Understand the need
- Integration of NAM data with traditional data
- Fit-for-purpose applications
- Transparency
- Stakeholder engagement, communication, and education
- Build confidence and understanding
  - Outreach and training
  - Hand's on use

EPA CompTox Chemicals Dashboard

Publicly available chemistry, toxicity, and exposure information for over 875,000 chemicals



Chemical characterization

- Physico-chemical properties (*in vitro* and/or *in silico*)
- Lists
- *In silico* read-across

Hazard—dose and effect

- *In vivo* animal legacy data
- *In vitro* assays
- Public literature
- Ecotoxicology (separate tools not on the dashboard)
  - Environmental toxicity data on aquatic life, terrestrial plants, and wildlife (ECOTOX knowledgebase)
  - Sequence alignment to predict across species susceptibility (SeqAPASS)

Toxicokinetics

- High-throughput *in vitro* and *in silico* parameters and model outputs from *in vitro* to *in vivo* extrapolation (IVIVE)

Exposure

- Exposure predictions, biomonitoring, production volume, use categories

Thank You!

Nisha S. Sipes

sipes.nisha@epa.gov

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